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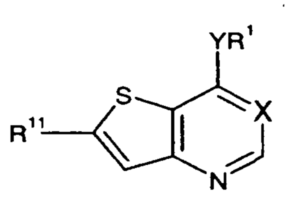
(54) Title: INDOLYL-UREA DERIVATIVES OF THIENOPYRIDINES USEFUL AS ANTI-ANGIOGENIC AGENTS, AND METHODS FOR THEIR USE



(I)

(57) Abstract: The invention relates to compounds represented by the formula FI and to prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds or said prodrugs, wherein X, R^1 and R^{11} are as defined herein. The invention also relates to pharmaceutical compositions containing the compounds of formula I and to methods of treating hyperproliferative disorders in a mammal by administering the compounds of formula I.

INDOLYL-UREA DERIVATIVES OF THIENOPYRIDINES USEFUL AS ANTIANGIOGENIC AGENTS, AND METHODS FOR THEIR USE

This application claims priority benefits under 35 U.S.C. § 119(e) of a United States Provisional Application No. 60/360,952, filed 1 March 2002, in its entirety for all purposes.

Field of the Invention

This invention relates to novel thienopyridine and thienopyridine derivatives that are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Background of the Invention

Compounds that are useful in the treatment of hyperproliferative diseases are also disclosed in the following patents and applications: PCT international patent application publication number WO 00/38665 (published July 6, 2001), PCT international patent application publication number WO 97/49688 (published December 31, 1997), PCT international patent application publication number WO 98/23613 (published June 4, 1998), United States patent application number 60/299,879 (filed June 21, 2001), United States patent application number 09/502,129 (filed February 10, 2000), United States patent application number 60/209,686 (filed June 6, 2000), United States patent application number 60/214,373 (filed June 28, 2000), United States patent application number 08/953,078 (filed October 17, 1997), United States Patent No. 6,071,935 issued June 6, 2000, PCT international patent application publication number WO 96/30347 (published October 3, 1996), PCT international patent application publication number WO 96/40142 (published December 19, 1996), PCT international patent application publication number WO 97/13771 (published April 17, 1997), and PCT international patent application publication number WO 95/23141 (published August 31, 1995). The foregoing patent and applications are incorporated herein by reference in their entirety.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e., a gene that upon activation leads to the formation of malignant tumor cells). Many oncogenes encode proteins that are aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the overexpression of a normal proto oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

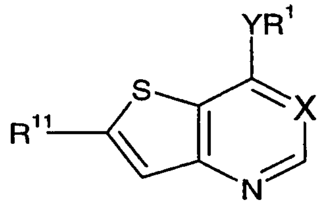
Receptor tyrosine kinases are large enzymes that span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion that functions as a kinase to phosphorylate a specific tyrosine residue in proteins and hence to influence cell proliferation. The foregoing tyrosine kinases may be classified as growth factor receptor (e.g. EGFR, PDGFR, FGFR and erbB2) or non-receptor (e.g. c-src and bcr-abl) kinases. It is known that such kinases are often aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. Aberrant erbB2 activity has been implicated in breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers. It has also been shown that epidermal growth factor receptor (EGFR) is mutated or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid cancers. Thus, it is believed that inhibitors of receptor tyrosine kinases, such as the compounds of the present invention, are useful as selective inhibitors of the growth of mammalian cancer cells.

It has also been shown that EGFR inhibitors may be useful in the treatment of pancreatitis and kidney disease (such as proliferative glomerulonephritis and diabetes-induced renal disease), and may reduce successful blastocyte implantation and therefore may be useful as a contraceptive. See PCT international application publication number WO 95/19970 (published July 27, 1995), hereby incorporated by reference in its entirety.

It is known that polypeptide growth factors such as vascular endothelial growth factor (VEGF) having a high affinity to the human kinase insert-domain-containing receptor (KDR) or the murine fetal liver kinase 1 (FLK-1) receptor have been associated with the proliferation of endothelial cells and more particularly vasculogenesis and angiogenesis. See PCT international application publication number WO 95/21613 (published August 17, 1995), hereby incorporated by reference in its entirety. Agents, such as the compounds of the present invention, that are capable of binding to or modulating the KDR/FLK-1 receptor may be used to treat disorders related to vasculogenesis or angiogenesis such as diabetes, diabetic retinopathy, age related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

Summary Of The Invention

A compound represented by the formula **I**



I

wherein

X is –CH- or –N-;

Y is –NH-, -O-, -S-, or $-CH_2-$;

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -C(O)(C_1-C_6 alkyl), C_6-C_{10} aryl or a 5 to 13 membered heterocyclic, wherein said C_6-C_{10} aryl and 5 to 13 membered heterocyclic groups are unsubstituted or substituted with 1 to 5 R^5 substituents;

each R^5 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^9$, $-SO_2NR^6R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkylamino, $-(CH_2)_jO(CH_2)_qNR^6R^7$, $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, $-S(O)_j(C_1\text{-}C_6$ alkyl), $-(CH_2)_t(C_6\text{-}C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t(C_6\text{-}C_{10}$ aryl), $-(CH_2)_tO(CH_2)_j(C_6\text{-}C_{10}$ aryl), $-(CH_2)_tO(CH_2)_q$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_jNR^7(CH_2)_qNR^9C(O)R^8$, $(CH_2)_jNR^7(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_jNR^7(CH_2)_qS(O)_j(C_1\text{-}C_6$ alkyl), $-(CH_2)_jNR^7(CH_2)_tR^6$, $-SO_2(CH_2)_t(C_6\text{-}C_{10}$ aryl), and $-SO_2(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the $-(CH_2)_q-$ and $-(CH_2)_t-$ moieties of the said R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 6, and the alkyl, aryl and heterocyclic moieties of the said R^5 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_tNR^6R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6\text{-}C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

each R^6 and R^7 is independently selected from H, OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6\text{-}C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tCN(CH_2)_tOR^9$, $-(CH_2)_tCN(CH_2)_tR^9$ and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6

and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H, $-OR^6$, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl; and,

R^{11} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)NR^{12}R^{13}$, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tNR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$ and $-CO_2R^{12}$, wherein t is an integer from 0 to 6, wherein said C_1-C_6 alkyl, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic) moieties of the said R^{11} groups are unsubstituted or substituted by one or more R^5 groups;

each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^5, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl rings are unsubstituted or substituted with one or more R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen;

or prodrugs thereof, or pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

In another embodiment of the compound of formula **I** R^{11} is $-(CH_2)_t$(5 to 10 membered heterocyclic), $-C(O)NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$ and $-CO_2R^{12}$, wherein t is an integer

from 0 to 6, wherein said R^{11} group $-(CH_2)_t$(5 to 10 membered heterocyclic) is unsubstituted or substituted by one or more R^5 groups and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of said R^{12} and R^{13} groups are unsubstituted or substituted by one or more substituents independently selected from R^5, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted by one or more R^5 substituents, where said R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

In another embodiment of the compound of formula **I** R^{11} is $-(CH_2)_t$(5 to 10 membered heterocyclic), and $-C(O)NR^{12}R^{13}$, wherein t is an integer from 0 to 6, wherein said R^{11} group $-(CH_2)_t$(5 to 10 membered heterocyclic) is unsubstituted or substituted with one or more R^5 groups and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of said R^{12} and R^{13} groups are unsubstituted or substituted by one or more substituents independently selected from R^5, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted with one or more R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

In still another embodiment of the compound of formula **I** R^{11} is $-C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^5, or R^{12} and R^{13} are

taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

In another embodiment of the compound of formula **I** R^{11} is -C(O)N$R^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents.

In still another preferred embodiment of the compound of formula **I** R^{11} is -C(O)N$R^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents.

In still another preferred embodiment of the compound of formula **I** R^{11} is -C(O)N$R^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl rings are unsubstituted or substituted with 1 to 5 R^5 substituents.

In another preferred embodiment of the compound of formula **I** R^{11} is -C(O)N$R^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl or piperidinyl ring, wherein said pyrrolidinyl or piperidinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents.

In another preferred embodiment of the compound of formula **I** R^{11} is -C(O)N$R^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl ring, wherein said pyrrolidinyl is unsubstituted or substituted with 1 to 5 R^5 substituents.

In another preferred embodiment of the compound of formula **I** R^{11} is $-C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidin-1-yl ring, wherein said pyrrolidin-1-yl is unsubstituted or substituted by 1 to 5 R^5 substituents.

In another preferred embodiment of the compound of formula **I** R^{11} is $-(CH_2)_t$(5 to 10 membered heterocyclic) group, wherein t is an integer from 0 to 6, said $-(CH_2)_t$(5 to 10 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

In another preferred embodiment of the compound of formula **I** R^{11} is $-(CH_2)_t$(5-8 membered heterocyclic) group, wherein t is an integer from 0 to 6, said $-(CH_2)_t$(5-8 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

In another preferred embodiment of the compound of formula **I** R^{11} is $-(CH_2)_t$(5 or 6 membered heterocyclic) group, wherein t is an integer from 0 to 6, said $-(CH_2)_t$(5 or 6 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

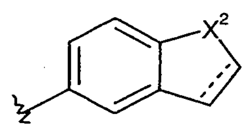
In another preferred embodiment of the compound of formula **I** R^{11} is $-(CH_2)_t$(5 membered heterocyclic) group, wherein t is an integer from 0 to 6, said $-(CH_2)_t$(5 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

In another preferred embodiment the compound of formula **I** R^{11} is $-(CH_2)_t$thiazolyl, wherein t is an integer from 0 to 6, said $-(CH_2)_t$thiazolyl is unsubstituted or substituted by 1 to 5 R^5 groups.

In another preferred embodiment, the compound of formula **I**, R^{11} is a thiazolyl, said thiazolyl is unsubstituted or substituted by 1 to 5 R^5 groups.

In another preferred embodiment, the compound of formula **I**, R^{11} is an imidazolyl, said imidazolyl is unsubstituted or substituted by 1 to 5 R^5 groups.

Other preferred compounds include those of formula **I** wherein R^1 is phenyl unsubstituted or substituted with 1 to 5 R^5 substituents, or R^1 is a group of the formula



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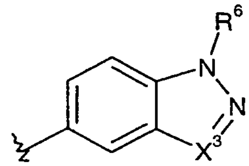

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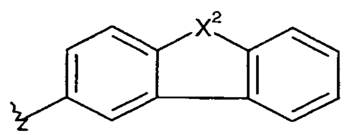

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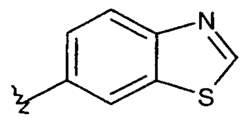
or



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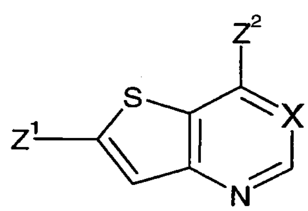
wherein X^2 is -S- or -N(R^6)-, X^3 is N or CH, the dashed line in formula **3** represents an optional double bond, and the above R^1 groups of formulas **3** and **5** are unsubstituted or substituted with 1 to 5 R^5 substituents and the R^1 groups of formulas **4** and **6** are unsubstituted or substituted with 1 to 3 R^5 substituents. Specifically preferred compounds include those wherein R^1 is a group of formula **3** above wherein said group is unsubstituted or substituted by 1 to 5 R^5 substituents.

The present invention also relates to intermediate compounds of the formula **II**

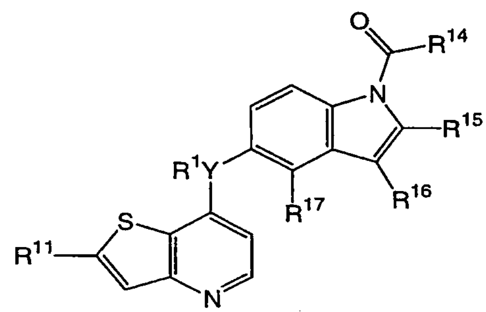


II

and to pharmaceutically acceptable salts thereof, wherein:

Z^1 is halo, -CO_2H, -$CONH_2$, -$CSNH_2$ and Z^2 is -OR^1; or Z^1 is R^{11} and Z^2 is halo; or Z^1 and Z^2 are each independently halo; X is N or CH; and wherein R^1 and R^{11} are as defined for said compounds of formula **I**. The above intermediates of formula **III** may be used to prepare the above compounds of formula **I**.

A compound represented by the formula **III**



III

wherein:

Y is –NH-, -O-, -S-, -CH_2-;

R^{14} is C_1-C_6 alkyl, C_1-C_6 alkylamino, C_3-C_{10} cycloalkylamino, or methylureido;

R^{15}, R^{16} and R^{17} are independently H, halo, or C_1-C_6 alkyl group; and

R^{11} is a heteroaryl group unsubstituted or substituted by one or more halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -NR^6C(O)R^7, -C(O)NR^6R^7, -NR^6R^7, -OR^9, -SO_2NR^6R^7, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_j$O$(CH_2)_q$NR^6R^7, -$(CH_2)_t$O$(CH_2)_q$OR^9, -$(CH_2)_t$OR^9, -S$(O)_j$(C_1-C_6 alkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$O$(CH_2)_j$(C_6-C_{10} aryl), -$(CH_2)_t$O$(CH_2)_q$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_j$N$R^7$$(CH_2)_qNR^6R^7$, -$(CH_2)_jNR^7$$CH_2$C(O)N$R^6R^7$,-$(CH_2)_jNR^7$$(CH_2)_qNR^9$C(O)$R^8$,$(CH_2)_jNR^7$$(CH_2)_tO(CH_2)_qOR^9$, -$(CH_2)_jNR^7$$(CH_2)_qS(O)_j$($C_1$-$C_6$ alkyl), -$(CH_2)_j$NR^7 -$(CH_2)_t$$R^6$, -$SO_2$$(CH_2)_t$($C_6$-$C_{10}$ aryl), and -$SO_2$$(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the -$(CH_2)_q$- and -$(CH_2)_t$- moieties of the said R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 6, and the alkyl, aryl and heterocyclic moieties of the said R^5 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -NR^6C(O)R^7, -C(O)NR^6R^7, -$(CH_2)_t$NR^6R^7, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_t$O$(CH_2)_q$OR^9, and -$(CH_2)_t$OR^9, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

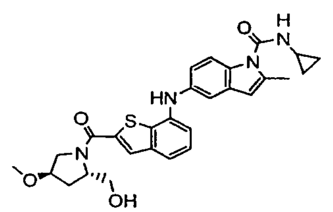
R^6 and R^7 is independently selected from H, OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_t$O$(CH_2)_q$OR^9, and -

$(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl; or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

Specific embodiments of the present invention include the following compounds: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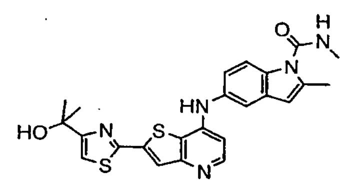

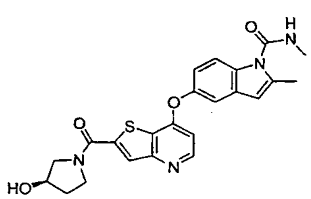
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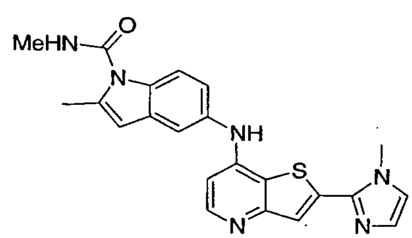
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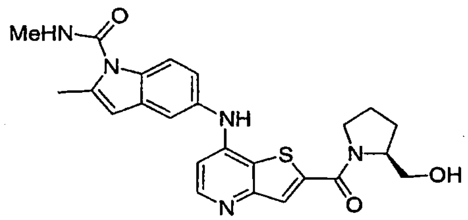

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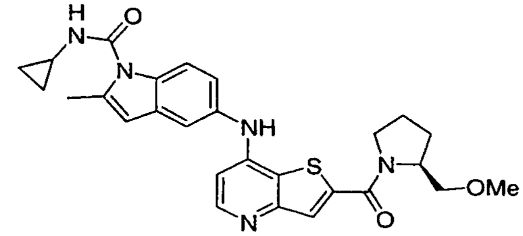

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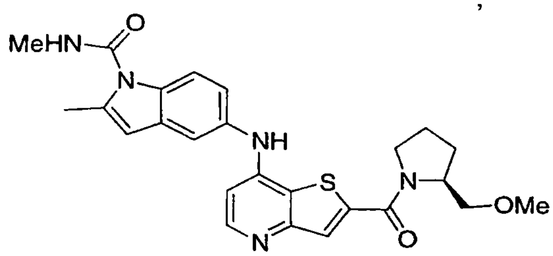

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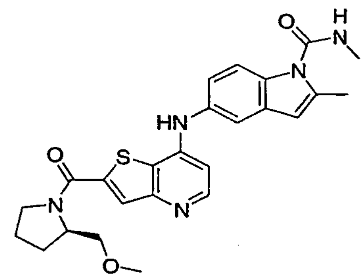

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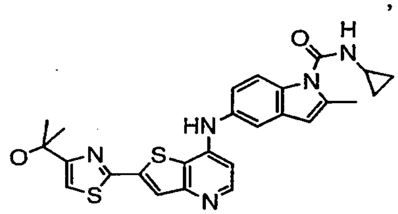

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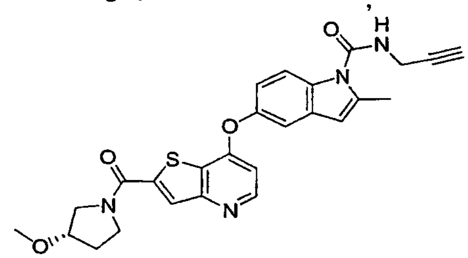

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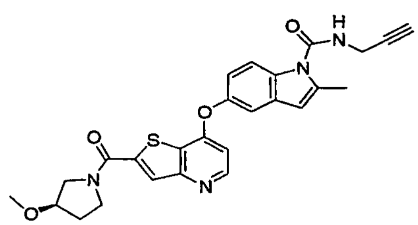

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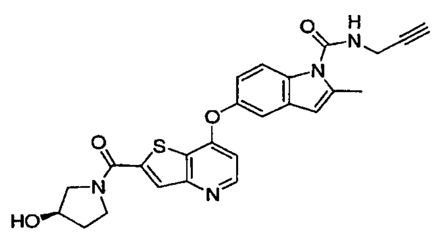

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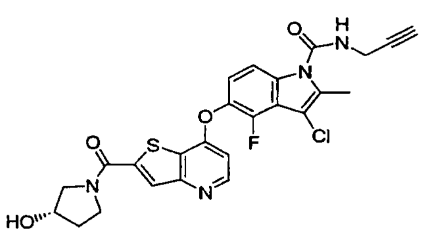

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or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

This invention also relates to pharmaceutical compositions containing and methods for treating abnormal cell growth through administering prodrugs of compounds of the formula **I**. Compounds of formula **I** having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs.

The invention also relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for the treatment of cancer such as brain, lung, ophthalmic, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, oesophageal, gynecological or thyroid cancer. In another embodiment, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., benign prostatic hypertropy (BPH)).

The invention also relates to a pharmaceutical composition for the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal which comprises a therapeutically effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the prevention of blastocyte implantation in a mammal which comprises a therapeutically effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, excema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

The invention also relates to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of the compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs. In one embodiment, said method relates to the treatment of cancer such as brain, ophthalmic, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer. In another embodiment, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., benign prostatic hypertropy (BPH)).

The invention also relates to a method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

The invention also relates to a method of treating pancreatitis or kidney disease in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

The invention also relates to a method of preventing blastocyte implantation in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

The invention also relates to a method of treating diseases related to vasculogenesis or angiogenesis in a mammal which comprises administering to said mammal an effective amount of a compound of formula **I**, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs. In one embodiment, said method is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, excema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

Patients that can be treated with the compounds of formula **I**, and prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis, BPH, lung cancer, eye cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphona, spinal axis tumors, brain stem gliomas or pituitary adenomas).

This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula **I** as defined above, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, that is effective in inhibiting farnesyl protein transferase, and a pharmaceutically acceptable carrier.

This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of formula **I**, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, in combination with an amount of a chemotherapeutic, wherein the amounts of the compound, salt, solvate, or prodrug, and of the chemotherapeutic are together effective in inhibiting abnormal cell growth. Many chemotherapeutics are presently known in the art. In one embodiment, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, *e.g.* anti-androgens.

This invention further relates to a method for inhibiting abnormal cell growth in a mammal which method comprises administering to the mammal an amount of a compound of formula **I**, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, in combination with radiation therapy, wherein the amount of the compound,

salt, solvate or prodrug is in combination with the radiation therapy effective in inhibiting abnormal cell growth in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

It is believed that the compounds of formula I can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of formula I or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, solvate or prodrug in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

This invention also relates to a method of and to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of formula I, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, or an isotopically-labelled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of formula **1** and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889

(published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in the present invention are Prinomastat, RO 32-3555, RS 13-0830, and the compounds recited in the following list: 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino] - propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4 - carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1 -hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4-[4-(4-chloro-phenoxy) - benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; (R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl) - amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid; 3-exo-3-[4 -(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8 -oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and (R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide; and pharmaceutically acceptable salts and solvates of said compounds.

Other anti-angiogenesis agents, including other COX-II inhibitors and other MMP inhibitors, can also be used in the present invention.

A compound of formula **I**, can also be used with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors, such as VEGF receptors and molecules that can inhibit VEGF; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA).

EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein. EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusetts). These and other EGFR-inhibiting agents can be used in the present invention.

VEGF inhibitors, for example SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined with the compound of the present invention. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal

antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California). These and other VEGF inhibitors can be used in the present invention as described herein.

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), can furthermore be combined with the compound of the invention, for example those indicated in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with the compounds of the present invention.

The compounds of the invention can also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, and the like. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula **I**, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and

pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula **I**, **II**, or **III** of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of formula **I** and their pharmaceutically acceptable salts and solvates can each independently also furthermore be used in a palliative neo-adjuvant/adjuvant therapy in alleviating the symptoms associated with the diseases recited herein as well as the symptoms associated with abnormal cell growth. Such therapy can be a monotherapy or can be in a combination with chemotherapy and/or immunotherapy.

The terms "abnormal cell growth" and "hyperproliferative disorder" are used interchangeably in this application.

"Abnormal cell growth", as used herein, refers to cell growth that is independent of normal regulatory mechanisms (*e.g.*, loss of contact inhibition), including the abnormal growth of normal cells and the growth of abnormal cells. This includes, but is not limited to, the abnormal growth of: (1) tumor cells (tumors), both benign and malignant, expressing an activated Ras oncogene; (2) tumor cells, both benign and malignant, in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs. Examples of such benign proliferative diseases are psoriasis, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis. "Abnormal cell growth" also refers to and includes the abnormal growth of cells, both benign and malignant, resulting from activity of the enzyme farnesyl protein transferase.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such

term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, refers to the act of treating, as “treating” is defined immediately above.

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, means saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties. Said “alkyl” group may include an optional carbon-carbon double or triple bond where said alkyl group comprises at least two carbon atoms. It is understood that for cyclic moieties at least three carbon atoms are required in said alkyl group.

The term "alkoxy", as used herein, unless otherwise indicated, means O-alkyl groups wherein "alkyl" is as defined above.

The term "aryl", as used herein, unless otherwise indicated, means an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The terms "5 membered heterocyclic", "5 or 6 membered heterocyclic", "5 to 8 membered heterocyclic", "5 to 10 membered heterocyclic" or "5 to 13 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 5, 6, 5 to 8, 5 to 10 or 5 to 13 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. An example of a 5 membered heterocyclic group is thiazolyl, an example of a 10 membered heterocyclic group is quinolinyl, and an example of a 13 membered heterocyclic group is a carbazole group. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, piperidino, morpholino, thiomorpholino and piperazinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl and thiazolyl. Heterocyclic groups having a fused benzene ring include benzimidazolyl, benzofuranyl, and benzo[1,3]dioxolyl.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, means salts of acidic or basic groups which may be present in the compounds or prodrugs of formula **I**. The compounds and prodrugs of formula **I** that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds and prodrugs of formula **I** are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide,

hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds and prodrugs of the formulas **I** that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and particularly, the sodium and potassium salts.

The compounds of the present invention may have asymmetric carbon atoms. Such diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomer mixtures and pure enantiomers are considered as part of the invention.

The compounds of present invention may in certain instances exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

The term "prodrug", as used herein, unless otherwise indicated, means compounds that are drug precursors, which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form).

Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula **I**. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters,

dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in Advanced Drug Delivery Reviews, 1996, 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in J. Med. Chem. 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

It will be appreciated that any solvate (e.g. hydrate) form of compounds of formula **I** and prodrugs thereof can be used for the purpose of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The terms "comprising" and "including" are used herein in their open, non-limiting sense.

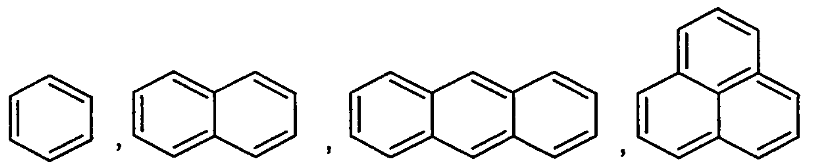
The term "alkyl" as used herein refers to straight- and branched-chain alkyl groups having from one to twelve carbon atoms. Exemplary alkyl groups include methyl (Me), ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like.

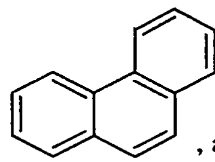
The term "heteroalkyl" as used herein refers to straight- and branched-chain alkyl groups having from one to twelve atoms containing one or more heteroatoms selected from S, O, and N.

The term "alkenyl" refers to straight- and branched-chain alkenyl groups having from two to twelve carbon atoms. Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, and the like.

The term "alkynyl" refers to straight- and branched-chain alkynyl groups having from two to twelve carbon atoms. Illustrative alkynyl groups include prop-2-ynyl, but-2-ynyl, but-3-ynyl, 2-methylbut-2-ynyl, hex-2-ynyl, and the like.

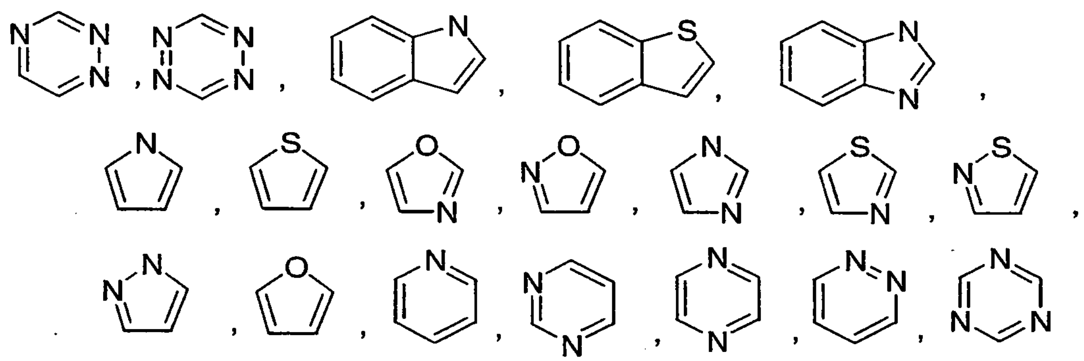
The term "aryl" (Ar) refers to monocyclic and polycyclic aromatic ring structures containing only carbon and hydrogen. Illustrative examples of aryl groups include the following moieties:

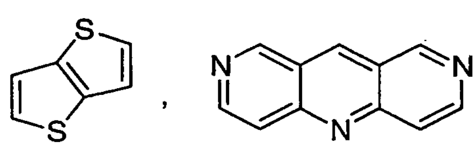




, and the like.

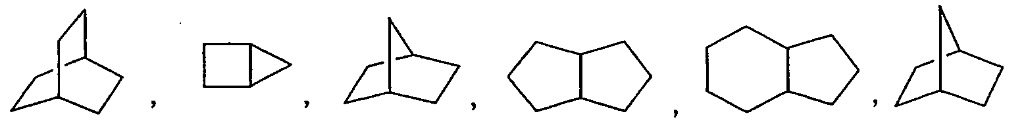
The term "heteroaryl" (heteroAr) refers to monocyclic and polycyclic aromatic ring structures which include one or more heteroatoms selected from nitrogen, oxygen and sulfur. The polycyclic heteroaryl group may be fused or non-fused. Illustrative examples of aryl groups include the following moieties:

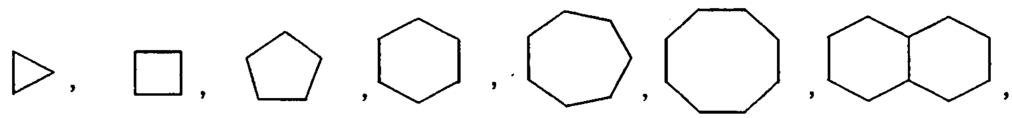


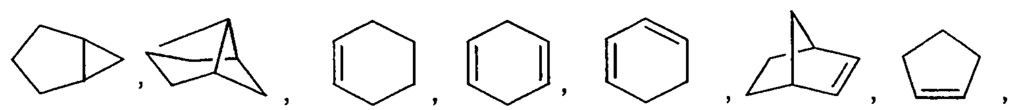


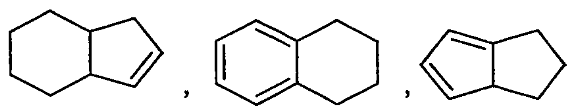
, and the like.

The term "cycloalkyl" refers to a monocyclic or polycyclic radical which may be saturated or unsaturated and contains carbocycles having from three to twelve carbon atoms, including bicyclic and tricyclic cycloalkyl structures. Illustrative examples of cycloalkyl groups include the following moieties:



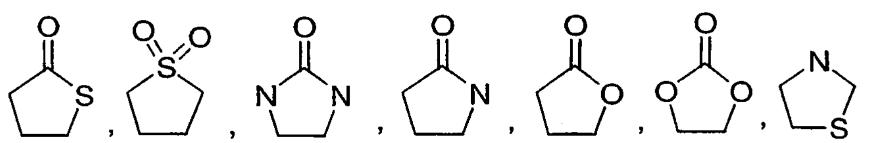


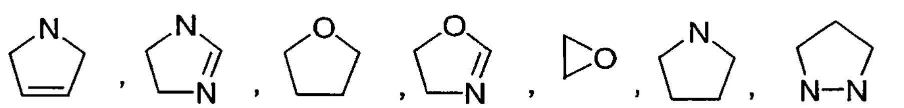


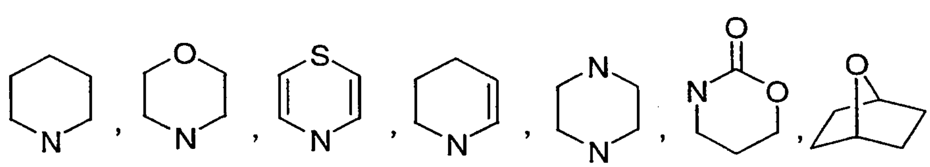


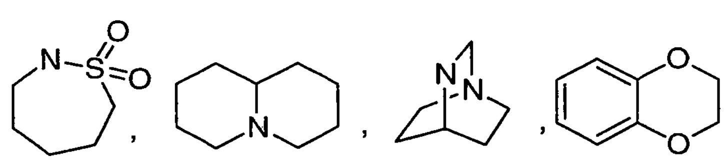
, and compounds of the like.

A "heterocycloalkyl" group refers to a monocyclic or polycyclic radical which may be saturated or unsaturated and contains from three to twelve ring atoms, selected from carbon and heteroatoms, preferably 4 or 5 ring carbon atoms, and at least one heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups include,









, and the like.

The term "heterocyclic" comprises both heterocycloalkyl and heteroaryl groups.

The term "alkoxy" refers to the radical –O-R where R is an alkyl as defined above. Examples of alkoxy groups include methoxy, ethoxy, propoxy, and the like.

The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

The term "alcohol" refers to the radical –R-OH where R is alkyl, alkenyl, alkynyl, Ar, heteroaryl, heterocycloalkyl, or cycloalkyl as defined above. Examples of alcohols include methanol, ethanol, propanol, phenol and the like.

The term "acyl" represents –C(O)R, -C(O)OR, -OC(O)R or -OC(O)OR where R is alkyl, alkenyl, alkynyl, Ar, heteroaryl, heterocycloalkyl, or cycloalkyl as defined as above.

The term "amide" refers to the radical –C(O)N(R')(R") where R' and R" are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, -OH, alkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl as defined above; or R' and R'' cyclize together with the nitrogen to form a heterocycloalkyl or heteroaryl as defined above.

The term "substituted" as used herein means that the group in question , e.g., alkyl group, etc., may bear one or more substituents.

The alkyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl groups and the substituents containing these groups, as defined hereinabove, may be optionally substituted by at least one other substituent. The term "optionally substituted" is intended to expressly indicate that the specified group is unsubstituted or substituted by one or more substituents from the list above. Various groups may be unsubstituted or substituted (i.e., they are optionally substituted) as indicated.

If the substituents themselves are not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent

into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

Some of the inventive compounds may exist in various stereoisomeric or tautomeric forms. The present invention encompasses all such cell proliferation-inhibiting compounds, including active compounds in the form of single pure enantiomers (i.e., essentially free of other stereoisomers), racemates, mixtures of enantiomers and/or diastereomers, and/or tautomers. Preferably, the inventive compounds that are optically active are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound having one chiral center (i.e., one asymmetric carbon atom) is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure.

Preferably, the compounds of the present invention are used in a form that is at least 90% optically pure, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

Additionally, the formulae are intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I includes compounds of the indicated structure in both hydrated and non-hydrated forms. Additional examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

In addition to compounds of Formula I, the invention includes pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds and metabolites.

The term "pharmaceutically acceptable" means pharmacologically acceptable and substantially non-toxic to the subject being administered the agent.

"A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound. "A pharmaceutically active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. Prodrugs and active metabolites of a compound may be

identified using routine techniques known in the art. See, e.g., Bertolini et al., *J. Med. Chem.*, 40, 2011-2016 (1997); Shan et al., *J. Pharm. Sci.*, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.*, 34, 220-230 (1995); Bodor, *Advances in Drug Res.*, 13, 224-331 (1984); Bundgaard, *Design of Prodrugs* (Elsevier Press 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

"A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic

acid, such as benzoic acid, 2-acetoxybenzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid, methanesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, carbonates, bicarbonates, primary, secondary, and tertiary amines, and cyclic amines, such as benzylamines, pyrrolidines, piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

Pharmaceutical compositions according to the invention may, alternatively or in addition to a compound of Formula I, comprise as an active ingredient pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds and metabolites. Such compounds, prodrugs, multimers, salts, and metabolites are sometimes referred to herein collectively as "active agents" or "agents."

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

Therapeutically effective amounts of the active agents of the invention may be used to treat diseases mediated by modulation or regulation of protein kinases. An "effective amount" is intended to mean that amount of an agent that significantly inhibits proliferation and/or prevents de-differentiation of a eukaryotic cell, e.g., a mammalian, insect, plant or fungal cell, and is effective for the indicated utility, e.g., specific therapeutic treatment.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. "Treating" is intended to mean at least the mitigation of a disease condition in a subject such as mammal (e.g., human), that is affected, at least in part, by the activity of one or more kinases, for example protein kinases such as tyrosine kinases, and includes: preventing the disease

condition from occurring in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but has not yet been diagnosed as having it; modulating and/or inhibiting the disease condition; and/or alleviating the disease condition.

Agents that potently regulate, modulate, or inhibit cell proliferation are preferred. For certain mechanisms, inhibition of the protein kinase activity associated with CDK complexes, among others, and those which inhibit angiogenesis and/or inflammation are preferred. The present invention is further directed to methods of modulating or inhibiting protein kinase activity, for example in mammalian tissue, by administering an inventive agent. The activity of agents as anti-proliferatives is easily measured by known methods, for example by using whole cell cultures in an MTT assay. The activity of the inventive agents as modulators of protein kinase activity, such as the activity of kinases, may be measured by any of the methods available to those skilled in the art, including in vivo and/or in vitro assays. Examples of suitable assays for activity measurements include those described in International Publication No. WO 99/21845; Parast et al., *Biochemistry*, 37, 16788-16801 (1998); Connell-Crowley and Harpes, *Cell Cycle: Materials and Methods*, (Michele Pagano, ed. Springer, Berlin, Germany)(1995); International Publication No. WO 97/34876; and International Publication No. WO 96/14843. These properties may be assessed, for example, by using one or more of the biological testing procedures set out in the examples below.

The active agents of the invention may be formulated into pharmaceutical compositions as described below. Pharmaceutical compositions of this invention comprise an effective modulating, regulating, or inhibiting amount of a compound of Formula I or Formula II and an inert, pharmaceutically acceptable carrier or diluent. In one embodiment of the pharmaceutical compositions, efficacious levels of the inventive agents are provided so as to provide therapeutic benefits involving anti-proliferative ability. By “efficacious levels” is meant levels in which proliferation is inhibited, or controlled. These compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

An inventive agent can be administered in conventional dosage form prepared by combining a therapeutically effective amount of an agent (e.g., a compound of Formula I) as an active ingredient with appropriate pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be either a solid or liquid. Exemplary of solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

A variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension.

To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of an inventive agent can be dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I is dissolved in DMSO and diluted with water. The composition may also be in the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

It will be appreciated that the actual dosages of the agents used in the compositions of this invention will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests in view of the experimental data for an agent. For oral administration, an exemplary daily dose generally employed is from about 0.001 to about 1000 mg/kg of body weight, with courses of treatment repeated at appropriate intervals. Administration of prodrugs is typically dosed at weight levels that are chemically equivalent to the weight levels of the fully active form.

The compositions of the invention may be manufactured in manners generally known for preparing pharmaceutical compositions, e.g., using conventional techniques such as

mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, which may be selected from excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

Proper formulation is dependent upon the route of administration chosen. For injection, the agents of the invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of agents.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the agents in admixture with fillers such as

lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions take the form of tablets or lozenges formulated in conventional manners.

For administration intranasally or by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the agents in water-soluble form. Additionally, suspensions of the agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

For administration to the eye, the agent is delivered in a pharmaceutically acceptable ophthalmic vehicle such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, for example, the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The

pharmaceutically acceptable ophthalmic vehicle may be an ointment, vegetable oil, or an encapsulating material. A compound of the invention may also be injected directly into the vitreous and aqueous humor.

Alternatively, the agents may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, the agents may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

An exemplary pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semi-permeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials

have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Some of the compounds of the invention may be provided as salts with pharmaceutically compatible counter ions. Pharmaceutically compatible salts may be formed with many acids, including hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free-base forms.

The agents of the invention may be useful in combination with known anti-cancer treatments such as: DNA interactive agents such as cisplatin or doxorubicin; topoisomerase II inhibitors such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents such as paclitaxel, docetaxel or the epothilones; hormonal agents such as tamoxifen; thymidilate synthase inhibitors such as 5-fluorouracil; and anti-metalbolites such as methotrexate. They may be administered together or sequentially, and when administered sequentially, the agents may be administered either prior to or after administration of the known anticancer or cytotoxic agent.

The agents may be prepared using the reaction routes and synthesis schemes as described below, employing the general techniques known in the art using starting materials that are readily available. The preparation of preferred compounds of the present invention is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other anti-proliferatives or protein kinase inhibitors of the invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or generally known in the art will be recognized as having applicability for preparing other compounds of the invention.

EXAMPLES

In the examples described below, unless otherwise indicated, all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company or Lancaster Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dichloromethane, toluene, and dioxane were purchased from Aldrich in Sure seal bottles and used as received. All solvents were purified using standard methods readily known to those skilled in the art, unless otherwise indicated.

The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F 254 plates Analtech (0.25 mm) and eluted with the appropriate solvent ratios (v/v), and are denoted where appropriate. The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

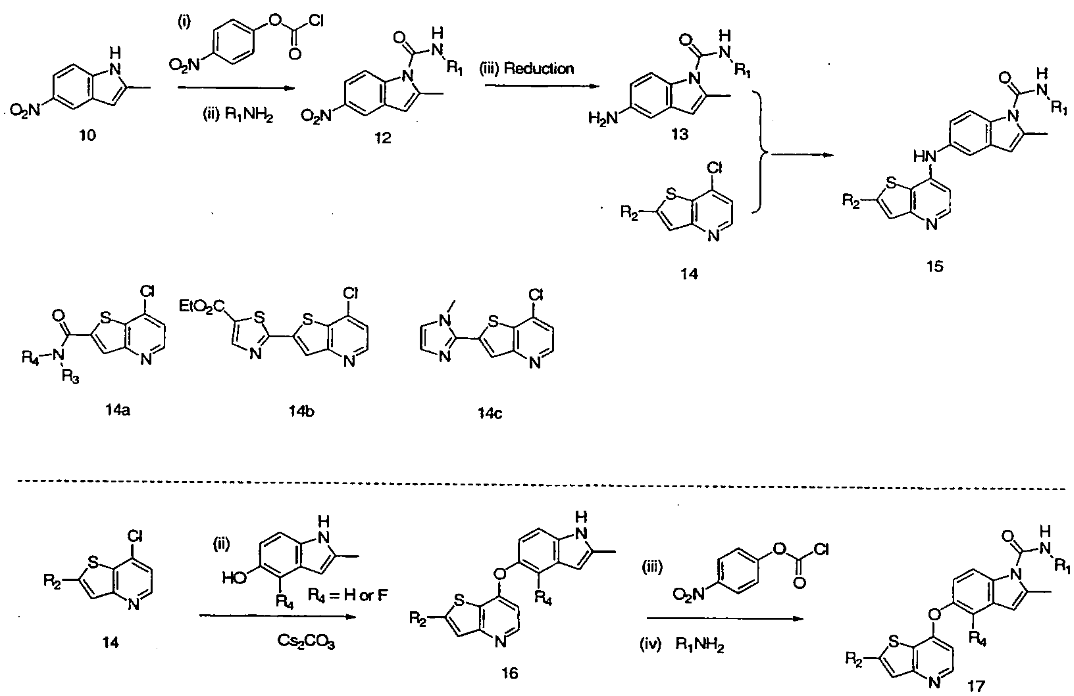
Visualization of the TLC plates was done with a *p*-anisaldehyde spray reagent or phosphomolybdic acid reagent (Aldrich Chemical 20 wt % in ethanol) and activated with heat. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated. Product solutions were dried over anhydrous Na_2SO_4 prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo*. Flash column chromatography (Still et al., *J. Org. Chem.*, 43, 2923 (1978)) was done using Baker grade flash silica gel (47-61 μm) and a silica gel: crude material ratio of about 20:1 to 50:1 unless otherwise stated. Hydrogenolysis was done at the pressure indicated in the examples or at ambient pressure.

^{1}H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz and ^{13}C-NMR spectra were recorded operating at 75 MHz. NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or CD_3OD (3.4 and 4.8 ppm and 49.3 ppm), or internally tetramethylsilane (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m

(multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as $CDCl_3$ solutions, and when given are reported in wave numbers (cm^{-1}). The mass spectra were obtained using LSIMS or electrospray. All melting points (mp) are uncorrected.

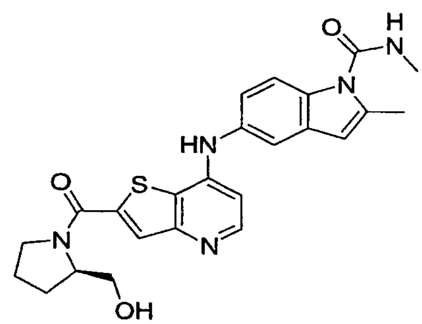
In one general synthetic process, compounds of Formula **I** are prepared according to the following reaction scheme:



5-Nitroindole (compound **10**) is treated with a base, e.g. NaH in THF or NaOH in organic/aqueous mixture and a reactive carbonate coupling reagent, e.g. p-nitrophenol chloroformate, phosgene, triphosgene. The resulting activated carbamate is treated with a suitable R_1 amine to give compounds of formula **12**. Alternatively, the anion of **10** may be treated with a suitable R_1 isocyanate to give compounds of formula **12**. Reduction of compounds of formula **12**, preferably with Pd/C under H_2 or with $SnCl_2$ gives compounds of formula **13**. Compounds of formula **13** and **14** are combined by heating them in solvent such as DMSO, isopropanol or ethanol/dichloroethane mixtures to produce compounds of formula

15. Alternatively, 5-hydroxy indoles, which are known in the literature, are combined with compounds of formula **14** by heating in DMSO with base, preferable Cs_2CO_3, to form compounds of formula **16**. Compounds of formula **16** are treated with a base, e.g. NaH or NaOH in organic/aqueous mixture and a reactive carbonate coupling reagent, e.g. p-nitrophenol chloroformate, phosgene, triphosgene. The resulting activated carbamate is treated with a suitable R_1 amine to give compounds of formula **17**. Alternatively, the anion of **16** may be treated with a suitable R_1 isocyanate to give compounds of formula **17**. Alternatively to using compounds of formula **14a,** compounds of formula **14** where R_2 is a carboxylic acid may be used in the coupling reaction that generates compounds of formula **15**. Amide formation may then be the final step.

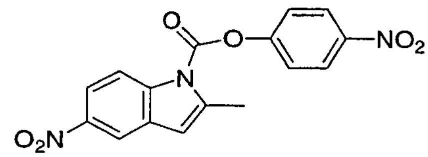
Example 1(a): 5-[2-(2R-Hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



To a solution of (7-chloro-thieno[3,2,b]pyridin-2-yl)-(2R-hydroxymethyl-pyrrolidin-1-yl)-methanone (59 mg 0.2 mmol), prepared in step (iv) below, and 5-amino-2-methylindole-1-carboxylic acid methylamide (45 mg, 0.22 mmol), prepared in step (iii) below, in 3 mL ethanol and 0.3 mL dichloroethane was added 4.0 M HCl in dioxane (0.05 mL, 0.2 mmol). The solution was heated to reflux under argon for 24 hours and was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with 5% methanol in dichloromethane to render 50 mg desired product as yellow solid (54 % yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.20 (d, 1H, J = 5.68 Hz), 7.75 (s, 1H), 7.65 (d, 1H, J = 8.79 Hz), 7.38 (d, 1H, J = 1.83 Hz), 7.13 (dd, 1H, J = 8.79, 2.01 Hz), 6.74 (d, 1H, J = 5.68 Hz), 6.33 (s, 1H), 4.32 (m, 1H), 3.71-3.90 (m, 4H), 3.00 (s, 3H), 2.53 (s, 3H), 1.90-2.12 (m, 4H). MS (ESI+) [M+H]/z Calc'd 464, found 464. Anal. ($C_{24}H_{25}N_5O_3S{\bullet}0.8H_2O$) C, H, N.

The starting materials were prepared as follows:

2-methyl-5-nitro-1-(4-nitrophenoxycarbonyl)indole



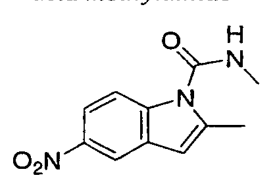
Method A:

To a stirred slurry of NaH (1.92 g of a 60% mineral oil dispersion, 48 mmole) in THF (120 ml) at -5°, under argon, was cautiously added 2-methyl-5-nitroindole (7.05 g, 40 mmole), in portions, as the solid. The reaction mixture was stirred at 0° for 40 minutes, then transferred, via cannula, to a solution of 4-nitrophenyl chloroformate (9.44 g, 47 mmole) in THF (60 ml). The resultant reaction mixture was stirred at ambient temperature for 15 hours prior to removal of the solvent by concentration, *in vacuo*. The residue obtained was suspended in EtOAc (200 ml), then filtered and washed with EtOAc and Et_2O to give 11.51 g (84%) of a pale yellow solid.

Method B:

To a stirred solution of 2-methyl-5-nitroindole (1.76 g, 10 mmole) in CH_2Cl_2 (90 ml) were added, sequentially, freshly crushed NaOH (1.20 g, 30 mmole), Bu_4NBr (32 mg, catalytic amount) and 4-nitrophenyl chloroformate (2.02 g, 10 mmole). After stirring at ambient temperature for 30 minutes, the reaction mixture was filtered and the filtrate was concentrated, *in vacuo*, to provide 2.89 g (85%) of a yellow solid. ^{1}H NMR (DMSO-d6): δ 8.51 (1H, d, J = 2.3 Hz), 8.41 (2H, d, J = 9.1 Hz), 8.27 (1H, d, J = 9.2 Hz), 8.17 (1H, dd, J = 2.3, 9.2 Hz), 7.80 (2H, d, J = 9.1Hz), 6.85 (1H, s), 2.70 (3H, s). *Anal.* Calcd. for $C_{16}H_{11}N_3O_6$•1.9 NaCl: C, 42.48; H, 2.45; N, 9.29. Found: C, 42.46; H, 2.43; N, 9.32.

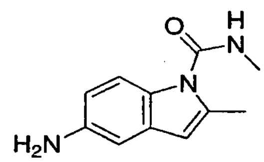
2-Methyl-5-nitro-indole-1-carboxylic acid methylamide



A 2.0 M solution of methylamine in THF (25 ml, 50 mmole) was added to a solution of 2-methyl-5-nitro-1-(4-nitrophenoxycarbonyl)indole **1a** (2.11 g, 6.2 mmole) in THF (240 ml). The resultant reaction mixture was stirred at ambient temperature for 4 hours prior to removal of the solvent by concentration, *in vacuo*. The residue obtained was partitioned between EtOAc (200 ml) and H_2O (200 ml). The layers were separated and the aqueous phase

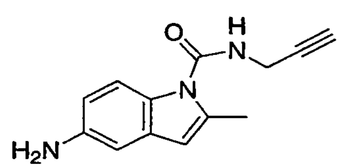
was extracted with EtOAc (2 x 100 ml). The combined organic extracts were washed with sat'd $NaHCO_3$ (150 ml), dried over Na_2SO_4 and concentrated, in vacuo, to give a yellow solid which was suspended in Et_2O (35 ml), filtered and washed with Et_2O (2 x 20 ml) to give 1.17 g (81%) of a pale yellow solid. ^1H NMR (DMSO-d6): δ 8.52 (1H, q, J = 4.5 Hz), 8.46 (1H, d, J = 2.3 Hz), 8.03 (1H, dd, J = 2.3, 9.1 Hz), 7.71 (1H, d, J = 9.1Hz), 6.62 (1H, s), 2.89 (3H, d, J = 4.5 Hz), 2.51 (3H, s). *Anal.* Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.56; H, 4.78; N, 17.82.

5-Amino-2-methyl-indole-1-carboxylic acid methylamide



Method A:

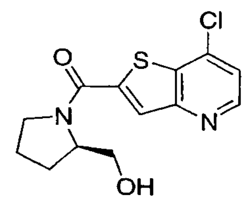
To a stirred solution of 2-methyl-5-nitroindole-1-carboxylic acid methylamide **1b** (1.30 g, 5.6 mmole) in EtOAc (50 ml) and THF (40 ml) was added 10% Pd on carbon (140 mg, ~10% wt. eq.). The resultant slurry was stirred under an H_2 atmosphere at ambient temperature for 90 minutes, then filtered through a pad of celite. The filtrate was subsequently concentrated, *in vacuo*, to give 1.2 g of an orange-brown resin which was purified by silica gel chromatography. Elution with CH_2Cl_2: CH_3OH (97:3) and evaporation of the appropriate fractions gave 0.99 g (88%) of a beige solid. ^1H NMR (DMSO-d6): δ 7.82 (1H, q, J = 4.5 Hz), 7.27 (1H, d, J = 8.7 Hz), 6.57 (1H, d, J = 2.1 Hz), 6.46 (1H, dd, J = 2.1, 8.7 Hz), 6.07 (1H, s), 4.64 (2H, br s), 2.81 (3H, d, J = 4.5 Hz), 2.40 (3H, s). *Anal.* Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.24; H, 6.34; N, 20.82.



Method B (used with hydrogenation sensitive substrates): A mixture of 5-nitro-2-methyl-indole-1-carboxylic acid prop-2-ynylamide (1.18 g, 4.23 mmol) and $SnCl_2 \bullet 2H_2O$ (3.34 g, 14.81 mmol) in EtOH (100 mL) was heated at 80°C for 10 hours. The mixture was cooled to room temperature. Saturated aqueous $NaHCO_3$ was added slowly. The mixture was then filtered through Celite, washed with EtOAc. The filtrate was extracted with EtOAc for three times. The combined organic layer was dried over Na_2SO_4, concentrated to give the crude

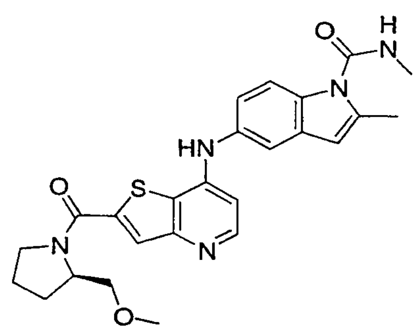
product. Elution with EtOAc and hexane (1:2) through a flash column and subsequent concentration provided the product as an orange solid (0.50 g, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (1H, d, J = 8.7 Hz), 6.77 (1H, d, J = 2.1 Hz), 6.62 (1H, d, J = 8.7, 2.3 Hz), 6.16 (1H, s), 5.77 (1H, bs), 4.31-4.23 (2H, m), 3.68 (2H, bs), 3.55 (3H, s), 2.36-2.30 (1H, m). LCMS (ESI+) [M+H]/z Calc'd 228, found 228.

(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(2R-hydroxymethyl-pyrrolidin-1-yl)-methanone



To a solution of pyrrolidin-2R-yl-methanol (1.12 g, 11 mmol) in 20 ml DMF was added 7-chloro-thieno[3,2-*b*]pyridine-2-carboxylic acid lithium salt (2.2 g, 10 mmol), followed by slow addition of HATU (4.2 g, 11 mmol) as solid. The mixture was stirred at room temperature for one hour and quenched with water. The mixture was then extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give crude product, which was further purified by flash column chromatography eluted with EtOAc : CH_2Cl_2 : MeOH (1:1:0.1) to give desired product as yellow oil (1.4 g 50% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73 (1H, d, J = 5.12 Hz), 8.09 (1H, s), 7.69 (1H, d, J = 5.13 Hz), 4.21 (1H, m), 3.86 (2H, m), 3.57 (2H, m), 1.90-2.10 (4H, m). MS (ESI+) [M+H]/z Calc'd 297, found 297.

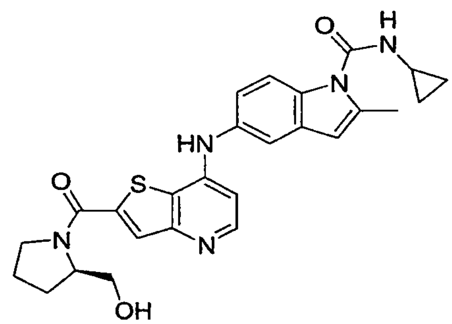
Example 1(b): 5-[2-(2R-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



Example 1(b) was prepared in a similar manner as Example 1(a) except that R-2-(methoxymethyl)pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.20 (1H, d, J = 5.68 Hz), 7.73 (1H, s), 7.65 (1H, d, J = 8.79

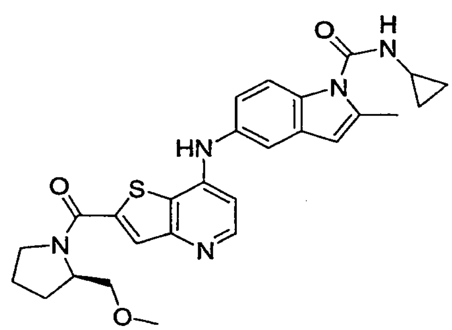
Hz), 7.38 (1H, d, J = 1.47 Hz), 7.12 (1H, dd, J = 8.79, 1.93 Hz), 6.74 (1H, d, J = 5.67 Hz), 6.33 (1H, s), 4.40 (1H, m), 3.85 (2H, m), 3.60 (2H, m), 3.36 (3H, s), 3.00 (3H, s), 2.53 (3H, s), 1.90-2.12 (4H, m). MS (ESI+) [M+H]/z Calc'd 478, found 478. Anal. ($C_{25}H_{27}N_5O_3S{\bullet}0.6H_2O$) C, H, N.

Example 1(c): 5-[2-(2R-Hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 1(c) was prepared in a similar manner as Example 1(a) except that cyclopropylamine was used instead of methylamine in step (ii). ^{1}H NMR (300 MHz, CD_3OD) δ 8.20 (1H, d, J = 3.48 Hz), 7.76 (1H, s), 7.59 (1H, d, J = 8.42 Hz), 7.38 (1H, s), 7.12 (1H, d, J = 8.79 Hz), 6.74 (1H, d, J = 4.19 Hz), 6.33 (1H, s), 4.32 (1H, m), 3.81 (4H, m), 2.88 (1H, m), 2.52 (3H, s), 2.02 (4H, m), 0.86 (2H, m), 0.73 (2H, m). MS (ESI+) [M+H]/z Calc'd 490, found 490. Anal. ($C_{26}H_{27}N_5O_3S{\bullet}0.5H_2O$) C, H, N.

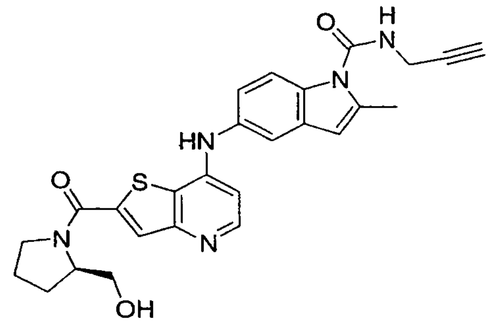
Example 1(d): 5-[2-(2R-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] py[illegible]in-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 1(d) was prepared in a similar manner as Example 1(b) ex[illegible] that cyclopropylamine was used instead of methylamine in step (ii). ^{1}H NMR (300 MHz, CD_3OD) δ 8.19 (1H, d, J = 5.5 Hz), 7.73 (1H, s), 7.58 (1H, d, J = 8.79 Hz), 7.37 (1H, s), 7.12 (1H, d, J = 8.79 Hz), 6.73 (1H, d, J = 5.5 Hz), 6.32 (1H, s), 4.40 (1H, m), 3.85 (2H, m), 3.60

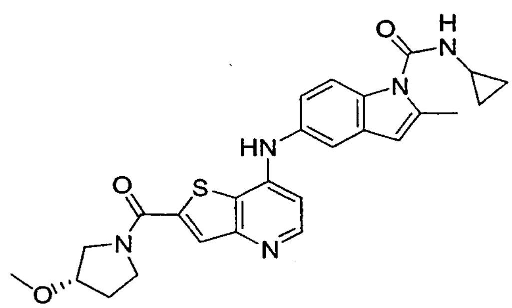
(2H, m), 3.36 (3H, s), 2.88 (1H, m), 2.51 (3H, s), 1.93-2.10 (4H, m), 0.86 (2H, m), 0.72 (2H, m). MS (ESI+) [M+H]/z Calc'd 504, found 504. Anal. ($C_{27}H_{29}N_5O_3S{\bullet}0.3H_2O$) C, H, N.

Example 1(e): 5-[2-(2R-Hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 1(e) was prepared in a similar manner as Example 1(a) except that propargylamine was used instead of methylamine in step (ii). [1]H NMR (300 MHz, DMSO-d_6) δ 8.84 (1H, s), 8.76 (1H, t, J = 5.46 Hz), 8.26 (1H, d, J = 5.27 Hz), 7.80 (1H, s), 7.62 (1H, d, J = 8.67 Hz), 7.37 (1H, d, J = 1.88 Hz), 7.10 (1H, dd, J = 8.67, 1.88 Hz), 6.71 (1H, d, J = 5.46 Hz), 6.38 (1H, s), 4.18 (1H, m), 4.11 (2H, m), 3.81 (2H, m), 3.50 (2H, m), 3.25 (1H, t, J = 2.26 Hz), 2.50 (3H, bs), 1.94 (4H, m). MS (ESI+) [M+H]/z Calc'd 488, found 488. Anal. ($C_{26}H_{25}N_5O_3S{\bullet}0.15CH_2Cl_2$) C, H, N.

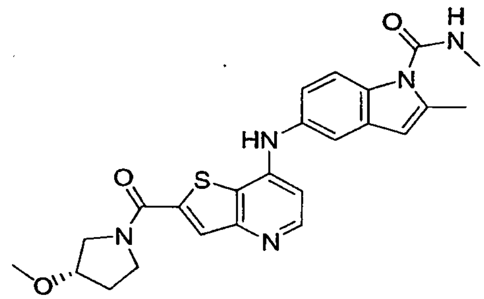
Example 1(f): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 1(f) was prepared in a similar manner as Example 1(c) except that 3S-methoxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). [1]H NMR (300 MHz, DMSO-d_6) δ 8.88 (1H, s), 8.55 (1H, s), 8.31 (1H, d, J = 5.31 Hz), 7.88 (1H, s), 7.57 (1H, d, J = 8.61 Hz), 7.39 (1H, s), 7.12 (1H, d, J = 8.42 Hz), 6.74 (1H, d, J = 5.31 Hz), 6.39 (1H, s), 3.84-4.10 (3H, m), 3.64 (2H, m), 3.31 (s, 1.5H), 3.28 (s, 1.5H), 2.88 (1H, m),

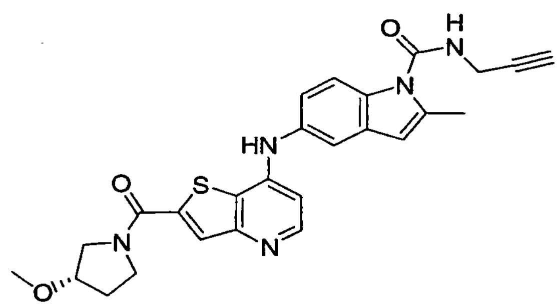
2.52 (3H, bs), 2.08 (2H, m), 0.80 (2H, m), 0.70 (2H, m). MS (ESI+) [M+H]/z Calc'd 490, found 490. Anal. ($C_{26}H_{27}N_5O_3S{\bullet}0.2H_2O$) C, H, N.

Example 1(g): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



Example 1(g) was prepared in a similar manner as Example 1(a) except that 3S-methoxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (1H, s), 8.29 (1H, d, J = 5.31 Hz), 8.22 (1H, d, J = 4.39 Hz), 7.85 (1H, s), 7.62 (1H, d, J = 8.79 Hz), 7.37 (1H, d, J = 1.28 Hz), 7.10 (1H, dd, J = 8.70, 1.74 Hz), 6.72 (1H, d, J = 5.49 Hz), 6.37 (1H, s), 3.79-4.10 (3H, m), 3.59 (2H, m), 3.28 (s, 1.5H), 3.25 (s, 1.5H), 2.89 (3H, bs), 2.50 (3H, bs), 2.02 (2H, m). MS (ESI+) [M+H]/z Calc'd 464, found 464. Anal. ($C_{24}H_{25}N_5O_3S{\bullet}1.0H_2O$) C, H, N.

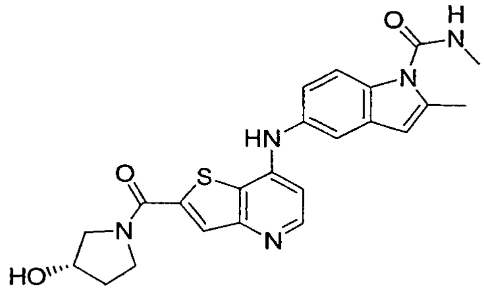
Example 1(h): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 1(h) was prepared in a similar manner as Example 1(e) except that 3S-methoxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (1H, s), 8.77 (1H, t, J = 5.40 Hz), 8.28 (1H, d, J = 5.31 Hz), 7.85 (1H, s), 7.63 (1H, d, J = 8.60 Hz), 7.37 (1H, s), 7.11 (1H, d, J = 8.61 Hz), 6.73 (1H, d, J = 5.49 Hz), 6.39 (1H, s), 4.11 (2H, d, J = 2.56 Hz), 4.09 (1H, m), 3.98 (2H, m), 3.84 (2H, m),

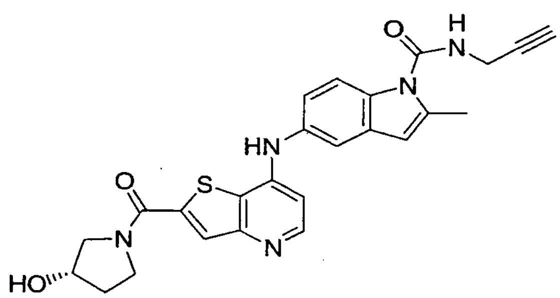
3.60 (1H, bs), 3.27 (s, 1.5H), 3.24 (s, 1.5H), 2.50 (3H, bs), 2.05 (2H, m). MS (ESI+) [M+H]/z Calc'd 488, found 488. Anal. ($C_{26}H_{25}N_5O_3S$) C, H, N.

Example 1(i): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



Example 1(i) was prepared in a similar manner as Example 1(a) except that 3S-hydroxyoxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.24 (1H, d, J = 5.7 Hz), 7.79 (1H, d, J = 18.1 Hz), 7.69 (1H, d, J = 8.7 Hz), 7.42 (1H, d, J = 2.1 Hz), 7.16 (1H, dd, J = 10.7, 2.1 Hz), 6.78 (1H, d, J = 5.7 Hz), 6.37 (1H, s), 4.50 (1H, bs), 4.08-3.97 (2H, m), 3.84-3.76 (2H, m), 3.76-3.67 (1H, m), 3.04 (3H, s), 2.56 (3H, s), 2.18-1.98 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 450, found 450. Anal. ($C_{23}H_{23}N_5O_3S$•0.8MeOH) C, H, N.

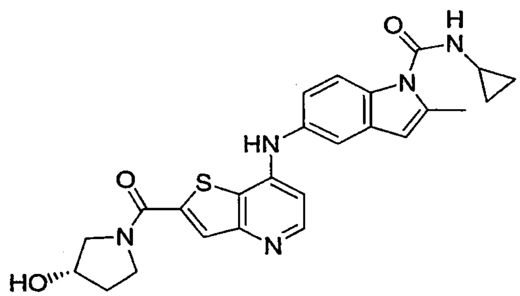
Example 1(j): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 1(j) was prepared in a similar manner as Example 1(e) except that 3S-hydroxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (1H, d, J = 5.7 Hz), 7.80 (1H, d, J = 18.3 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.43 (1H, d, J = 1.9 Hz), 7.18 (1H, d, J = 8.8, 2.1 Hz), 6.80 (1H, d, J = 5.8 Hz), 6.39 (1H, s), 4.53 (1H, bs), 4.24 (2H, d, J = 2.4 Hz), 4.06-3.98 (2H, m), 3.85-3.76 (2H, m), 3.76-3.68

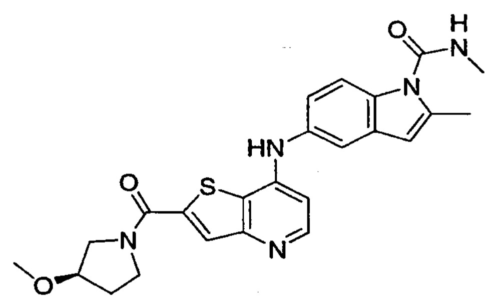
(1H, m), 2.77-2.72 (1H, m), 2.68 (3H, s), 2.19-2.02 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 474, found 474. Anal. ($C_{25}H_{23}N_5O_3S \bullet 1.0H_2O$) C, H, N.

Example 1(k): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 1(k) was prepared in a similar manner as Example 1(c) except that 3S-hydroxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.02 (1H, d, J = 5.6 Hz), 7.62 (1H, d, J = 17.7 Hz), 7.39 (1H, d, J = 8.8 Hz), 7.38 (1H, s), 7.20 (1H, s), 6.92 (1H, dd, J = 8.7, 2.1 Hz), 6.57 (1H, d, J = 5.5 Hz), 6.14 (1H, s), 4.30 (1H, bs), 3.90-3.70 (2H, m), 3.61-3.50 (2H, m), 3.50-3.45 (1H, m), 2.71-2.65 (1H, m), 2.32 (3H, s), 1.93-1.74 (2H, m), 0.68-0.60 (2H, m), 0.55-0.50 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 476, found 476. Anal. ($C_{25}H_{25}N_5O_3S \bullet 0.7CH_2Cl_2$) C, H, N.

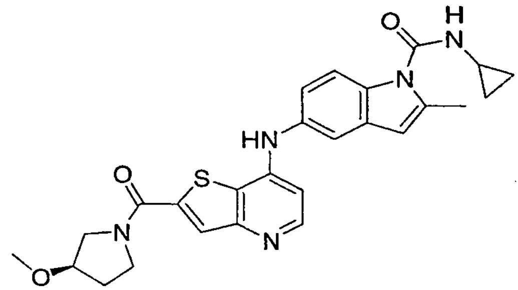
Example 1(l): 5-[2-(3R-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



Example 1(l) was prepared in a similar manner as Example 1(a) except that 3R-methoxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, d, J = 5.5 Hz), 7.76 (1H, d, J = 17.7 Hz), 7.70 (1H, d, J = [illegible] Hz), 7.40 (1H, s), 7.12 (1H, dd, J = 8.8, 2.4 Hz), 6.70 (1H, d, J = 5.5 Hz), 6.32 (1H, s), 6.17 (1H, d, J = 3.4 Hz), 6.16 (1H, s), 4.07-4.01 (1H, m), 3.98-3.87 (2H, m), 3.87-3.68 (2H, m),

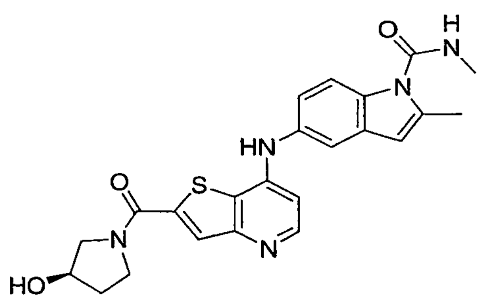
3.20 (3H, d, J = 14.5 Hz), 3.17 (3H, d, J = 3.4 Hz), 2.67 (3H, s), 2.35-2.04 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 464, found 464. Anal. ($C_{24}H_{25}N_5O_3S{\bullet}1.5H_2O$) C, H, N.

Example 1(m): 5-[2-(3R-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 1(m) was prepared in a similar manner as Example 1(c) except that 3R-methoxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.21 (1H, d, J = 5.5 Hz), 7.75 (1H, d, J = 5.5 Hz), 7.59 (1H, d, J = 8.5 Hz), 7.39 (1H, s), 7.13 (1H, dd, J = 8.8, 2.4 Hz), 6.77 (1H, d, J = 5.5 Hz), 6.47 (1H, s), 4.17-4.11 (1H, m), 4.02-3.87 (2H, m), 3.86-3.63 (2H, m), 3.37 (3H, d, J = 14.5 Hz), 2.95-2.85 (1H, m), 2.53 (3H, s), 2.30-2.02 (2H, m), 0.91-0.83 (2H, m), 0.77-0.70 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 490, found 490. Anal. ($C_{26}H_{27}N_5O_3S{\bullet}2.0H_2O$) C, H, N.

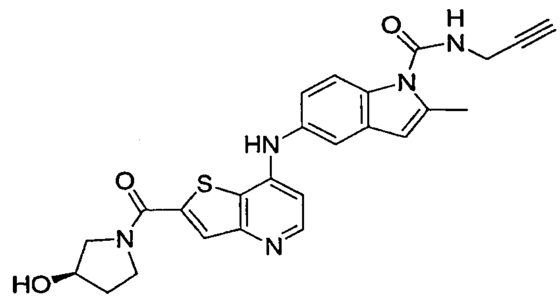
Example 1(n): 5-[2-(3R-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



Example 1(n) was prepared in a similar manner as Example 1(a) except that 3R-hydroxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (1H, d, J = 5.5 Hz), 7.77 (1H, d, J = 17.7 Hz), 7.67 (1H, d, J = 8.5 Hz), 7.42 (1H, s), 7.17 (1H, dd, J = 8.8, 2.4 Hz), 6.77 (1H, d, J = 5.5 Hz), 6.36 (1H, s), 4.57 (1H, bs), 4.08-3.98 (2H, m), 3.82-3.72 (2H, m), 3.71-3.67 (1H, m), 3.02 (3H, s), 2.57 (3H, s),

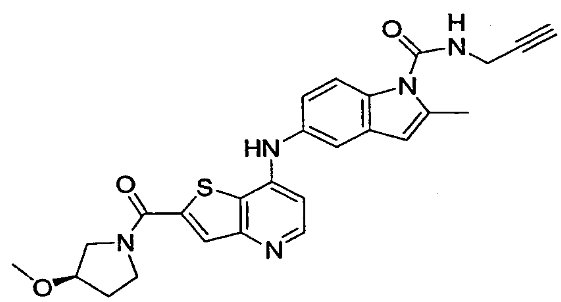
2.18-1.98 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 450, found 450. Anal. ($C_{23}H_{23}N_5O_3S$•1.2H_2O) C, H, N.

Example 1(o): 5-[2-(3R-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 1(o) was prepared in a similar manner as Example 1(e) except that 3R-hydroxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (1H, d, J = 5.5 Hz), 7.79 (1H, d, J = 17.7 Hz), 7.67 (1H, d, J = 8.5 Hz), 7.42 (1H, s), 7.19 (1H, dd, J = 8.8, 2.4 Hz), 6.82 (1H, d, J = 5.5 Hz), 6.39 (1H, s), 4.57 (1H, bs), 4.25 (2H, d, J = 1.9 Hz), 4.11-4.00 (2H, m), 3.86-3.77 (2H, m), 3.77-3.68 (1H, m), 2.78-2.72 (1H, m), 2.59 (3H, s), 2.32-2.02 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 474, found 474. Anal. ($C_{25}H_{23}N_5O_3S$•1.0MeOH•1.5H_2O) C, H, N.

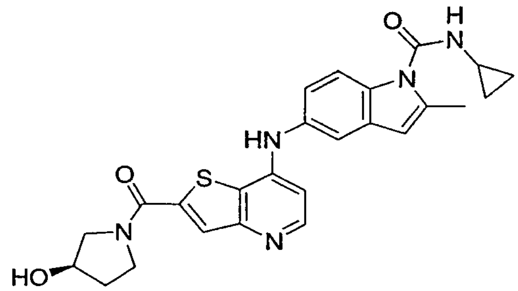
Example 1(p): 5-[2-(3R-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 1(p) was prepared in a similar manner as Example 1(e) except that 3R-methoxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.26 (1H, d, J = 5.5 Hz), 7.81 (1H, d, J = 5.5 Hz), 7.77 (1H, d, J = 8.5 Hz), 7.43 (1H, s), 7.18 (1H, dd, J = 8.8, 2.4 Hz), 6.79 (1H, d, J = 5.5 Hz), 6.49 (1H, s), 4.24 (2H, d, J = 1.9 Hz), 4.19-4.00 (2H, m), 4.05-3.88 (2H, m), 3.85-3.64 (1H, m), 3.38 (3H, d, J =

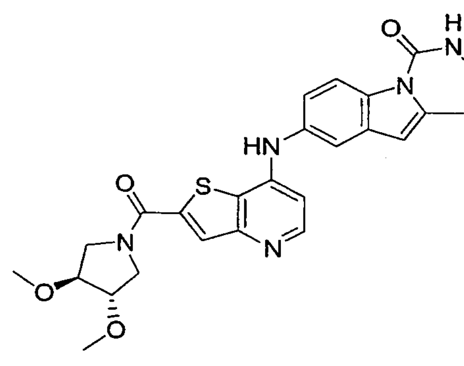
14.5 Hz), 2.78-2.72 (1H, m), 2.59 (3H, s), 2.32-2.02 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 488, found 488. Anal. ($C_{26}H_{25}N_5O_3S{\bullet}0.3H_2O$) C, H, N.

Example 1(q): 5-[2-(3R-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 1(q) was prepared in a similar manner as Example 1(c) except that 3R-hydroxy-pyrrolidine was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, DMSO-d6) δ 8.38 (1H, d, J = 3.2 Hz), 8.13 (1H, d, J = 5.3 Hz), 7.67 (1H, d, J = 19.9 Hz), 7.39 (1H, d, J = 8.7 Hz), 7.21 (1H, s), 6.94 (1H, d, J = 8.3 Hz), 6.57 (1H, dd, J = 8.7, 2.4 Hz), 6.21 (1H, s), 4.21 (1H, d, J = 15.4 Hz), 3.86-3.74 (2H, m), 3.53-3.38 (2H, m), 3.35-3.28 (1H, m), 2.74-2.66 (1H, m), 2.32 (3H, s), 1.85-1.74 (2H, m), 0.66-0.57 (2H, m), 0.56-0.49 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 476, found 476. Anal. ($C_{25}H_{25}N_5O_3S{\bullet}0.7HCl$) C, H, N.

Example 1(r): 5-[2-(3S,4S-Dimethoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide

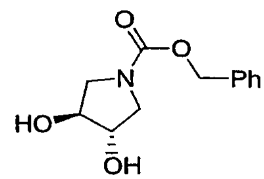


Example 1(r) was prepared in a similar manner as Example 1(a) except that 3S, 4S-dimethoxy-pyrrolidine, prepared as described below, was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.11 (1H, d, J = 5.65 Hz), 7.66 (1H, s), 7.56 (1H, d, J = 8.66 Hz), 7.29 (1H, s), 7.03 (1H, dd, J = 8.67, 2.07 Hz), 6.65 (1H, d, J = 5.65

Hz), 6.24 (1H, s), 3.77-3.91 (2H, m), 3.62-3.65 (2H, m), 3.32 (3H, s), 3.27 (3H, s), 3.19-3.21 (2H, m), 2.90 (3H, s), 2.43 (3H, s). MS (ESI+) [M+H]/z Calc'd 494, found 494. Anal. ($C_{25}H_{27}N_5O_4S{\bullet}1.0H_2O{\bullet}0.3CHCl_3$) C, H, N.

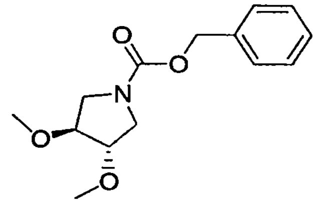
The starting materials were prepared as follows:

(i) 3S,4S-Dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester



Pd on C (300 mg) was added to a solution of (3S,4S)-(+)-benzyl-3,4-pyrrolidindiol (2.5 g, 12.9 mmol, commercially available) in MeOH. The reaction mixture was stirred under H_2 balloon overnight, filtered thought Celite and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (10 mL) and 6% Na_2CO_3 was added to adjust pH ~10. Benzyl chloroformate (3.69 mL, 25.87 mmol) was added to the reaction mixture (during addition of benzyl chloroformate, 6% Na_2CO_3 was added to adjust pH ~9). The reaction mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. The residue was taken into water (50 mL) and extracted with EtOAc (2x50 mL). The organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (2% CH_3OH in CH_2Cl_2) to give colorless oil (1.51 g, 51%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.34 (5H, m), 5.10 (1H, s), 4.12 (2H, m), 3.65-3.70 (2H, m), 3.36-3.43 (2H, m), 2.83 (1H, bs), 2.65 (1H, bs).

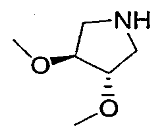
(ii) 3S,4S-Dimethoxy-pyrrolidine-1-carboxylic acid benzyl ester



To a solution of NaH (0.347 g, 8.67 mmol) in THF at 0°C was added 3S,4S-dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester (0.823 g, 3.47 mmol). The reaction mixture was stirred at room temperature for 20 min and then iodomethane (1.08 mL, 17.35 mmol) was added. The reaction mixture was stirred at room temperature overnight, quenched with H_2O (30 mL), extracted with EtOAc (2x25 mL). The organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2

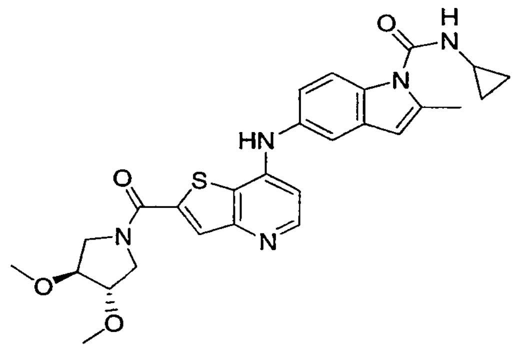
to 1% CH_3OH in CH_2Cl_2) to give colorless oil (0.639 g, 69%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.36 (5H, m), 5.12 (2H, s), 3.79 (2H, m), 3.50-3.55 (4H, m), 3.35 (s, 6H).

(iii) 3S,4S-Dimethoxy-pyrrolidine



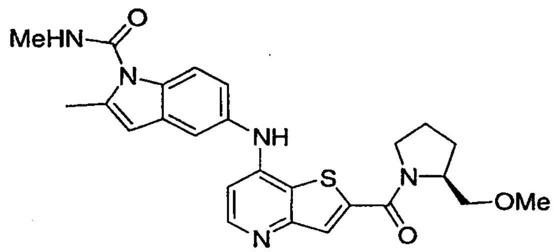
To a solution of 3S, 4S-dimethoxy-pyrrolidine-1-carboxylic acid benzyl ester (0.639 g, 2.41 mmol) in EtOAc was added 10% Pd on C (0.135 mg). The reaction mixture was stirred under H_2 Balloon overnight, filtered thought Celite and concentrated under reduced pressure. The residue was used without further purification.

Example 1(s): 5-[2-(3S,4S-Dimethoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



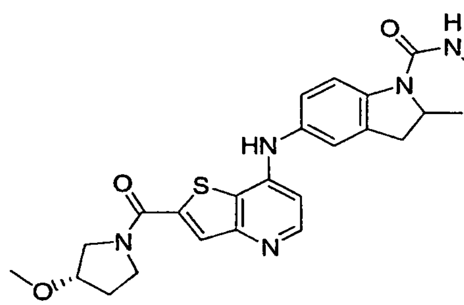
Example 1(s) was prepared in a similar manner as Example 1(r) except that cyclopropylamine was used in place of methylamine in step (ii). ^1H NMR (300 MHz, CD_3OD) δ 8.12 (1H, d, J = 5.65 Hz), 7.66 (1H, s), 7.59 (1H, d, J = 8.87 Hz), 7.29 (1H, d, J = 2.08 Hz), 7.03 (1H, dd, J = 8.66, 2.07 Hz), 6.65 (1H, d, J = 5.84 Hz), 6.23 (1H, s), 3.77-3.92 (4H, m), 3.33 (1H, s), 3.28 (3H, s), 3.19-3.20 (2H, m), 2.76-2.80 (1H, m), 2.41 (3H, s), 0.73-0.77 (2H, m), 0.62-0.65 (2H, m). MS (ESI+) [M+H]/z Calc'd 520, found 520. Anal. ($C_{27}H_{29}N_5O_4S \bullet 0.85H_2O$) C, H, N.

Example 1(t): 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b] pyridin-7-ylamino)-2-methylindole-1-carboxylic acid methylamide (2).



Example 1(t) was prepared in a similar manner as Example 1(a) except that S-2-methoxymethyl-pyrrolidine, was used instead of pyrrolidin-2R-yl-methanol in step (iv). ^{1}H NMR (DMSO-d$_6$): δ 10.09 (1H, br s), 8.54 (1H, d, J = 5.4 Hz), 8.27 (1H, q, J= 4.5 Hz), 8.00 (1H, s), 7.68 (1H, d, J = 9.0 Hz), 7.40 (1H, d, J = 2.4 Hz), 7.07 (1H, dd, J = 2.4, 9.0 Hz), 6.65 (1H, d, J = 5.4 Hz), 6.40 (1H, s), 4.36-4.25 (1H, m), 3.93-3.76 (2H, m), 3.59-3.38 (2H, m), 3.27 (3H, s), 2.88 (3H, d, J = 4.5 Hz), 2.48 (3H, s), 2.06-1.83 (4H, m). *Anal.* Calcd. for $C_{25}H_{27}N_5O_3S$•0.5 H_2O: C, 61.71; H, 5.80; N, 14.39. Found: C, 61.92; H, 5.79; N, 14.33.

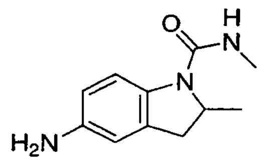
Example 1(u): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-2,3-dihydro-indole-1-carboxylic acid methylamide



Example 1(u) was prepared in a similar manner as Example 1(g) except that 5-amino-2-methyl-2,3-dihydro-indole-1-carboxylic acid methylamide, prepared as described below, was used instead of 5-amino-2-methyl-indole-1-carboxylic acid methylamide in the final step. ^{1}H NMR (300 MHz, CD_3OD) δ 8.21 (d, 1H, *J* = 5.5 Hz), 7.81 (d, 1H, *J* = 8.4 Hz), 7.75 (d, 1H, *J* = 6.4 Hz), 7.12 (s, 1H), 7.07 (d, 1H, *J* = 8.6 Hz), 6.73 (d, 1H, *J* = 5.7 Hz), 4.46 (m, 1H), 4.10 (m, 1H), 3.86-3.99 (m, 2H), 3.64-3.79 (m, 2H), 3.41 (m, 1H), 3.36 (s, 3H), 2.82 (s, 3H), 2.67 (d, 1H, *J* = 16 Hz), 2.02-2.25 (m, 2H), 1.25 (d, 3H, *J* = 6.0 Hz). MS (ESI+) [M+H]/z Calc'd 466, found 466. Anal. ($C_{24}H_{27}N_5O_3S$•0.4EtOAc•0.3H_2O) C, H, N.

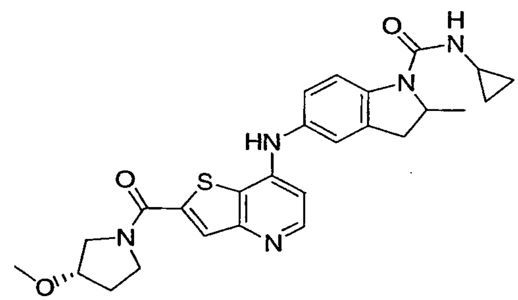
The starting material was prepared as follows:

(i) 5-Amino-2-methyl-2,3-dihydro-indole-1-carboxylic acid methylamide



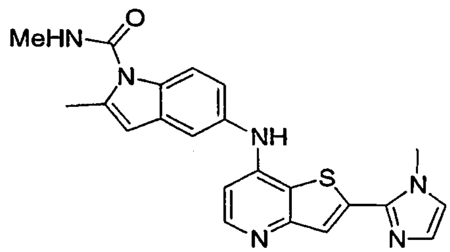
To a stirred solution of 2-methyl-5-nitro-indole-1-carboxylic acid methylamide (0.65 g, 2.78 mmol) in 20 mL EtOAc and 4 mL EtOH was added Pd on C (0.3 g, 10 % w/w). The mixture was stirred under H_2 balloon at room temperature for one hour and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with 1-3% MeOH in CH_2Cl_2 to give 140 mg 5-amino-2-methyl-indole-1-carboxylic acid methylamide (24% yield) together with 150 mg 5-amino-2-methyl-2,3-dihydro-indole-1-carboxylic acid methylamide (26% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.56 (d, 1H, J = 6.2 Hz), 6.65 (s, 1H), 6.58 (d, 1H, J = 6.1 Hz), 4.41 (m, 1H), 3.23-3.39 (m, 1H), 2.85 (s, 3H), 2.54 (d, 1H, J = 15.5 Hz), 1.20 (d, 3H, J = 6 Hz).

Example 1(v): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-2,3-dihydro-indole-1-carboxylic acid cyclopropylamide



Example 1(v) was prepared in a similar manner as Example 1(u) except that cyclopropylamine was used instead of methylamine in step (ii). ^{1}H NMR (300 MHz, CD_3OD) δ 8.20 (d, 1H, J = 5.5 Hz), 7.84 (d, 1H, J = 8.4 Hz), 7.73 (d, 1H, J = 6.0 Hz), 7.10 (s, 1H), 7.07 (d, 1H, J = 8.6 Hz), 6.74 (d, 1H, J = 5.7 Hz), 4.46 (m, 1H), 4.10 (m, 1H), 3.88-3.98 (m, 2H), 3.62-3.78 (m, 2H), 3.39 (m, 1H), 3.35 (s, 3H), 2.58-2.69 (m, 2H), 2.04-2.26 (m, 2H), 1.23 (d, 3H, J = 6.0 Hz), 0.74 (m, 2H), 0.57 (m, 2H). MS (ESI+) [M+H]/z Calc'd 492, found 492. Anal. ($C_{26}H_{29}N_5O_3S$•0.35EtOAc•0.4H_2O) C, H, N.

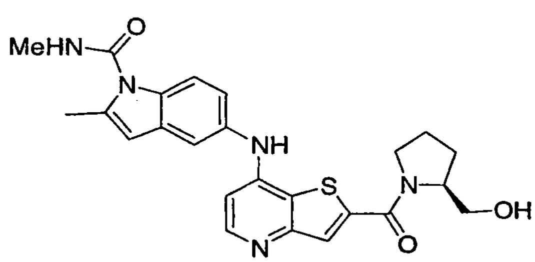
Example 2(a): 5-(2-[1-methyl-1H-imidazol-2-yl]thieno[3,2-b]pyridin-7-ylamino)-2-methylindole-1-carboxylic acid methylamide.



To a stirred slurry of 5-amino-2-methylindole-1-carboxylic acid methylamide (632 mg, 3.1 mmole), prepared in Example 1(a) step (iii), in 2-propanol (35 ml) was added 4.0 M HCl in 1,4-dioxane (0.75 ml, 3 mmole) followed by 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine (500 mg, 2 mmole), prepared as described in PCT application WO-99/24440, Example 149. The resultant solution was heated at reflux for 54 hours. After cooling to room temperature, the crude reaction mixture was poured into sat'd $NaHCO_3$ (150 ml), then diluted with water (50 ml). The precipitate that formed was collected by filtration, then washed with water (2 x 50 ml) and EtOAc (3 x 30 ml). The solid obtained was suspended in EtOAc (15 ml), filtered and washed with Et_2O (3 x 10 ml) to give 693 mg (83%) of a beige solid. ^{1}H NMR (DMSO-d6): δ 8.76 (1H, s), 8.22 (1H, d, J = 5.5 Hz), 8.20 (1H, q, J = 5.4 Hz), 7.68 (1H, s), 7.60 (1H, d, J = 8.7 Hz), 7.35 (1H, d, J = 0.2 Hz), 7.34 (1H, d, J = 1.9 Hz), 7.08 (1H, dd, J = 1.9, 8.7 Hz), 6.98 (1H, d, J = 0.2 Hz), 6.67 (1H, d, J = 5.5 Hz), 6.36 (1H, s), 3.94 (3H, s), 2.88 (3H, d, J = 5.4 Hz), 2.48 (3H, s). *Anal.* Calcd. for $C_{22}H_{20}N_6OS \bullet 1.0 H_2O$: C, 60.81; H, 5.10; N, 19.34; S, 7.38. Found: C, 60.53; H, 5.13; N, 19.07; S, 7.50.

Example 2(b): 5-(2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-ylamino)-2-methylindole-1-carboxylic acid methylamide.

Example 2(b) was prepared in a similar manner as Example 2(a) except that 7-chloro-2-[(S)-



2-([t-butyldimethylsilyloxy]methyl)-pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine, prepared as described below, was used instead of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine. ^{1}H NMR (DMSO-d6): δ 9.68 (1H, br s),8.33 (1H, d, J = 6.0 Hz), 8.26 (1H, q,

J= 4.5 Hz), 7.82 (1H, s), 7.65 (1H, d, J = 8.7 Hz), 7.42 (1H, d, J = 2.0 Hz), 7.12 (1H, dd, J = 2.0, 8.7 Hz), 6.77 (1H, d, J = 6.0 Hz), 6.39 (1H, s), 4.84 (1H, m), 4.23-4.04 (1H, m), 3.83-3.69 (2H, m), 3.59-3.38 (2H, m), 2.88 (3H, d, J = 4.5 Hz), 2.48 (3H, s), 2.05-1.79 (4H, m). *Anal.* Calcd. for $C_{24}H_{25}N_5O_3S \bullet 0.7\ H_2O$:: C, 60.54; H, 5.59; N, 14.71. Found: C, 60.72; H, 5.74; N, 14.53.

The starting materials were prepared as follows:

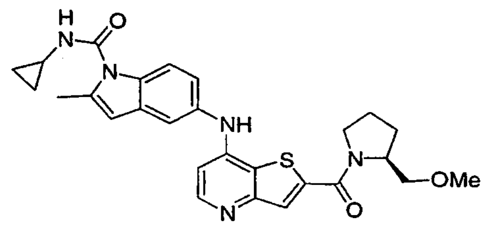
(i) 7-chloro-2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine.

This material was prepared by the coupling of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate and S-(+)-2-(hydroxymethyl)pyrrolidine in a manner as previously described for Example 1(a), step (iv) to give 4.95 g (55%) of an off-white solid. ^{1}H NMR (DMSO-d6): δ 8.72 (1H, d, J = 5.1 Hz), 8.08 (1H, s), 7.68 (1H, d, J = 5.1 Hz), 4.27-4.13 (1H, m), 3.94-3.73 (2H, m), 3.67-3.44 (2H, m), 2.09-1.79 (4H, m). *Anal.* Calcd. for $C_{13}H_{13}N_2O_2SCl$: C, 52.61; H, 4.42; N, 9.44; S, 10.80; Cl, 11.95. Found: C, 52.61; H, 4.52; N, 9.62; S, 10.59; Cl, 11.96.

(ii) 7-chloro-2-[(S)-2-([t-butyldimethylsilyloxy]methyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine.

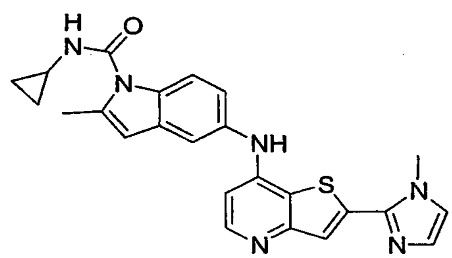
To a stirred solution of 7-chloro-2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine (4.50 g, 15 mmole) was added t-butyldimethylchlorosilane (3.18 g, 21 mmole) and triethylamine (3.4 ml, 2.47 g, 24 mmole). The resultant reaction mixture was stirred at ambient temperature for 16 hours. The crude reaction mixture was poured into water (150 ml) and extracted with CH_2Cl_2 (150 ml). The combined organic extracts were washed with brine (150 ml), dried over Na_2SO_4 and concentrated, *in vacuo*, to give 7.8 g of an orange syrup, which was purified by silica gel chromatography. Elution with Et_2O:hexane (67:33) and evaporation of the appropriate fractions gave 5.73 g (92%) of an off-white solid. . ^{1}H NMR (DMSO-d6): δ 8.72 (1H, d, J = 5.0 Hz), 8.07 (1H, s), 7.68 (1H, d, J = 5.0 Hz), 4.30-4.15 (1H, m), 3.94-3.67 (4H, m), 2.12-1.81 (4H, m), 0.85 (9H, s), 0.03 (3H, s), 0.00 (3H, s). *Anal.* Calcd. for $C_{19}H_{27}N_2O_2SClSi$: C, 55.52; H, 6.62; N, 6.82; S, 7.80; Cl, 8.63. Found: C, 55.49; H, 6.46; N, 6.92; S, 7.80; Cl, 8.88.

Example 2(c): 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b] pyridin-7-ylamino)-2-methylindole-1-carboxylic acid cyclopropylamide



Example 2(c) was prepared in a similar manner as Example 2(b) except that S-2-(methoxymethyl)pyrrolidine was used instead of 7 S-(+)-2-(hydroxymethyl)pyrrolidine in step (i) and cyclopropyl amine was used instead of methylamine in the referenced procedure for Example 1(a), step (ii). ^{1}H NMR (DMSO-d_6): δ 8.85 (1H, s), 8.50 (1H, d, J = 3.3 Hz), 8.26 (1H, d, J = 5.5 Hz), 7.80 (1H, s), 7.53 (1H, d, J = 8.7 Hz), 7.34 (1H, d, J = 1.9 Hz), 7.08 (1H, dd, J = 1.9, 8.7 Hz), 6.70 (1H, d, J = 5.5 Hz), 6.35 (1H, s), 4.37-4.21 (1H, m), 3.91-3.72 (2H, m), 3.59-3.47 (2H, m), 3.26 (3H, s), 2.88-2.79 (1H, m), 2.46 (3H, s), 2.06-1.81 (4H, m), 0.79-0.59 (4H, m). *Anal.* Calcd. for $C_{27}H_{29}N_5O_3S$•0.8 CH_3OH•0.1 CH_2Cl_2: C, 62.31; H, 6.07; N, 13.02; S, 5.96. Found: C, 62.38; H, 6.03; N, 12.84; S, 5.82.

Example 2(d): 5-(2-[1-methyl-1H-imidazol-2-yl]thieno[3,2-b]pyridin-7-ylamino)-2-

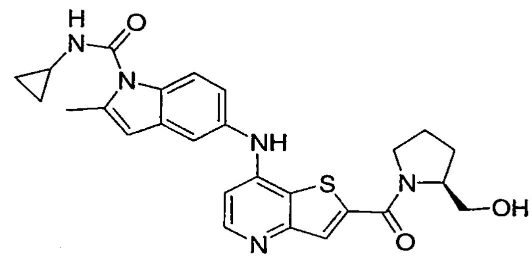


methylindole-1-carboxylic acid cyclopropylamide

Example 2(d) was prepared in a similar manner as Example 2(a) except that cyclopropyl amine was used instead of methylamine in the referenced procedure for Example 1(a), step (ii). ^{1}H NMR (DMSO-d_6): δ 8.78 (1H, s), 8.50 (1H, d, J = 3.2 Hz), 8.22 (1H, d, J = 5.5 Hz), 7.68 (1H, s), 7.53 (1H, d, J = 8.7 Hz), 7.35 (1H, d, J = 0.3 Hz), 7.34 (1H, d, J = 1.9 Hz), 7.08 (1H, dd, J = 1.9, 8.7 Hz), 6.98 (1H, d, J = 0.3 Hz), 6.67 (1H, d, J = 5.5 Hz), 6.35 (1H, s), 3.94 (3H, s), 2.88-2.79 (1H, m), 2.46 (3H, s), 0.79-0.62 (4H, m). *Anal.* Calcd. for

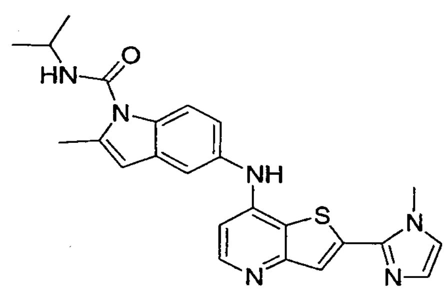
$C_{24}H_{22}N_6OS•0.6\ H_2O$: C, 63.58; H, 5.16; N, 18.54; S, 7.07. Found: C, 63.63; H, 5.19; N, 18.52; S, 7.02.

Example 2(e): 5-(2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b] pyridin-7-ylamino)-2-methylindole-1-carboxylic acid cyclopropylamide



Example 2(e) was prepared in a similar manner as Example 2(b) except that cyclopropylamine was used instead of methylamine in the referenced procedure for Example 1(a), step (ii). ^{1}H NMR (DMSO-d_6): δ 8.85 (1H, s), 8.51 (1H, d, J = 2.8 Hz), 8.27 (1H, d, J = 5.4 Hz), 7.80 (1H, s), 7.53 (1H, d, J = 8.6 Hz), 7.35 (1H, d, J = 1.5 Hz), 7.08 (1H, dd, J = 1.5, 8.6 Hz), 6.71 (1H, d, J = 5.4 Hz), 6.35 (1H, s), 5.11-4.76 (1H, m), 4.39-4.11 (1H, m), 3.91-3.72 (2H, m), 3.62-3.44 (2H, m), 2.88-2.78 (1H, m), 2.46 (3H, s), 2.08-1.79 (4H, m), 0.82-0.59 (4H, m). *Anal.* Calcd. for $C_{26}H_{27}N_5O_3S•0.75\ CH_2Cl_2$: C, 58.07; H, 5.19; N, 12.66; S, 5.80. Found: C, 58.08; H, 5.27; N, 12.44; S, 5.74.

Example 2(f): 5-(2-[1-methyl-1H-imidazol-2-yl]thieno[3,2-b]pyridin-7-ylamino)-2-methylindole-1-carboxylic acid isopropylamide



Example 2(f) was prepared in a similar manner to Example 2(a) except that 5-amino-2-methylindole-1-carboxylic acid cyclopropylamide, prepared as described below, was used instead of 5-amino-2-methylindole-1-carboxylic acid methylamide. ^{1}H NMR (DMSO-d_6): δ 8.76 (1H, s), 8.22 (1H, d, J = 5.5 Hz), 8.20 (1H, q, J = 5.4 Hz), 7.81(1H, d, J = 8.5 Hz), 7.68 (1H, s), 7.36 (1H, d, J = 0.2 Hz), 7.09 (1H, d, J = 1.5 Hz), 7.01 (1H, dd, J = 1.5, 8.5 Hz), 7.00 (1H, d, J = 0.2 Hz), 6.67 (1H, d, J = 5.5 Hz), 6.36, 6.34 (1H, s), 4.64-4.52 (1H, m), 3.95 (3H,

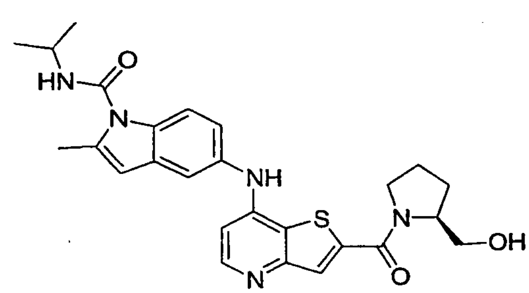
s), 2.88 (3H, d, J = 5.4 Hz), 2.64, 2.59 (3H, s) 1.14, 1.13 (6H, d, J = 6.6 Hz). *Anal.* Calcd. for $C_{22}H_{20}N_6OS \bullet 0.8\ H_2O \bullet 0.2\ Et_2O$: C, 62.87; H, 5.87; N, 17.74. Found: C, 62.91; H, 6.07; N, 17.70.

The starting materials were prepared as follows:

(i) **2-methyl-5-nitroindole-1-carboxylic acid cyclopropylamide.** A solution of 2.5 M n-butyllithium in hexanes (1.5 ml, 3.75 mmole) was added, dropwise, to a solution of 2-methyl-5-nitroindole (525 mg, 3 mmole) in THF (10 ml) at -75^0. This mixture was stirred for 20 minutes at -75^0 prior to addition of isopropyl isocyanate (3 ml, 2.60 g, 30 mmole). The cooling bath was removed and the reaction was stirred for a further 6 hours, then poured into water (20 ml) and extracted with ether (2 x 25 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, *in vacuo*. The residue obtained was triturated from hexane to give 690 mg (86%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.58 (1H, d, J = 7.2 Hz), 8.46(1H, d, J = 2.3 Hz), 8.03 (1H, dd, J = 2.3, 9.1 Hz), 7.65 (1H, d, J =9.1 Hz), 6.61 (1H, s), 4.10-3.88 (1H, m), 2.41 (3H, s), 1.23 (6H, d, J =6.6 Hz).

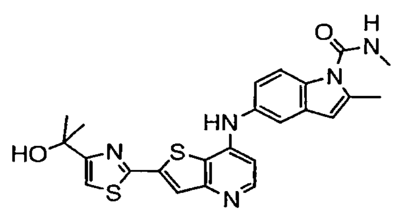
(ii) **5-amino-2-methylindole-1-carboxylic acid cyclopropylamide.** This material was prepared by the reduction of 2-methyl-5-nitroindole-1-carboxylic acid in a manner as previously described for Example 1(a), step (iii), method A. ^{1}H NMR (DMSO-d_6): δ 7.45 (1H, d, J = 8.4 Hz), 6.48 (1H, d, J= 1.2 Hz), 6.32 (1H, dd, J = 1.2, 8.4 Hz), 6.00, 5.98 (1H, s), 4.71-4.49 (2H, m), 3.95-3.77 (1H, m), 2.44, 2.39 (3H, s), 1.11, 1.10(6H, d, J = 6.7 Hz).

Example 2(g): 5-(2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b] pyridin-7-ylamino)-2-methylindole-1-carboxylic acid isopropylamide



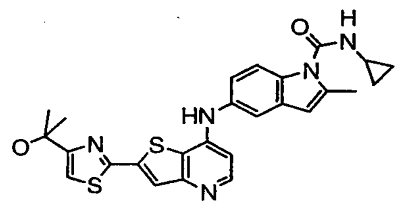
Example 2(g) was prepared in a similar manner as Example 2(b) except that 5-amino-2-methylindole-1-carboxylic acid cyclopropylamide was used instead of 5-amino-2-methylindole-1-carboxylic acid methylamide. ^{1}H NMR (DMSO-d_6): δ 8.81 (1H, s), 8.23(1H, d, J = 5.4 Hz), 7.72 (1H, s), 7.52 (1H, d, J = 8.6 Hz), 7.32 (1H, d, J = 1.5 Hz), 7.06 (1H, dd, J = 1.5, 8.6 Hz), 6.71 (1H, d, J = 5.4 Hz), 6.36, 6.34 (1H, s), 5.09-4.86 (1H, m), 4.63-4.53 (1H, m), 4.39-4.11 (1H, m), 3.93-3.74 (2H, m), 3.63-3.45 (2H, m), 2.46, 2.43 (3H, s), 2.06-1.76 (4H, m), 1.12, 1.10 (6H, d, J= 6.6 Hz). *Anal.* Calcd. for $C_{26}H_{29}N_5O_3S \bullet 2.2\ H_2O$: C, 58.78; H, 6.34; N, 13.18. Found: C, 58.82; H, 6.09; N, 12.78.

Example 3(a): 5-{2-[4-(1-Hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*] pyridin-7-ylamino}-2-methyl-indole-1-carboxylic acid methylamide



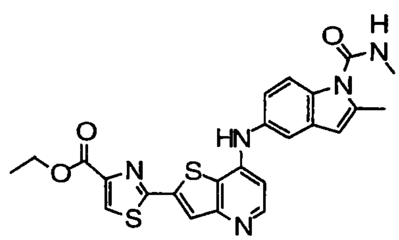
Example 3(a) was prepared in a similar manner to Example 1(a) except that the reaction was carried out in DMSO at 100°C and that 2-[2-(7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-thiazol-4-yl]-propan-2-ol, prepared in example 27 of section A of US Serial No. 60/209,686, filed June 6, 2000, hereby incorporated by reference in its entirety for all purposes, was used instead of (7-chloro-thieno[3,2,*b*]pyridin-2-yl)-(2R-hydroxymethyl-pyrrolidin-1-yl)-methanone. Purification was through a flash column eluting with EtOAc:CH_2Cl_2:MeOH (1:1:0.1) and subsequent concentration that provided the product as a yellow solid (0.48 g, 51% yield). HPLC: R_t 3.77 min. (95% area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 9.14 (1H, s), 8.43 (1H, d, *J* = 5.5Hz), 8.37 (1H, d, *J* = 4.3Hz), 8.09 (1H, s), 7.79 (1H, d, *J* = 8.5Hz), 7.71 (1H, s), 7.56 (1H, s), 7.28 (1H, d, *J* = 8.8Hz), 6.90 (1H, d, *J* = 5.5Hz), 6.54 (1H, s), 5.47 (1H, s), 3.05 (3H, d, *J* = 4.6Hz), 2.71 (3H, s), 1.66 (6H, s). HRMS (ESI) $C_{24}H_{23}N_5O_2S_2$ (M + H$^+$) *m/z*: Calc. 478.1377, Found 478.1392. Anal. ($C_{24}H_{23}N_5O_2S_2 \bullet 0.EtOAc$) Calc'd: C, 59.60; H, 5.41: N, 12.78. Found C, 59.57; H, 5.16; N, 12.90.

Example 3(b): 5-{2-[4-(1-Hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*] pyridin-7-ylamino}-2-methyl-indole-1-carboxylic acid cyclopropylamide



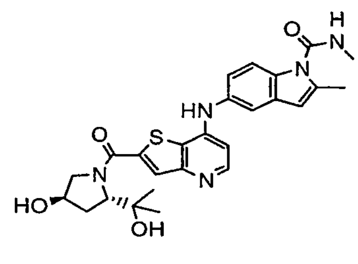
Example 3(b) was prepared in a similar manner to Example 3(a) except that cyclopropyl amine was used instead of methylamine (0.11 g, 40% yield). HPLC: R_t 3.98 min. (100% area). HRMS (ESI) $C_{26}H_{25}\ N_5O_2S_2$ (M + H^+) *m/z*: Calc. 504.1533, Found 504.1541. Anal. ($C_{26}H_{25}\ N_5O_2S_2$•$0.5H_2O$) Calc'd: C, 60.90; H, 5.11: N, 13.66. Found C, 61.25; H, 5.14; N, 13.45.

Example 3(c): 2-[7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-*b*]pyridin-2-yl]-thiazole-4-carboxylic acid ethyl ester



Example 3(c) was prepared in a similar manner to Example 3(a) except that 2-(7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-thiazole-4-carboxylic acid ethyl ester, prepared in example 26 of section C of PC10795A, was used instead of (7-chloro-thieno[3,2-*b*]pyridin-2-yl)-(2R-hydroxymethyl-pyrrolidin-1-yl)-methanone (0.0.42 g, 30% yield). HPLC: R_t 4.03 min. (100% area). HRMS (ESI) $C_{24}H_{23}N_5O_2S_2$ (M + H^+) *m/z*: Calc. 478.1377, Found 478.1392. Anal. ($C_{24}H_{21}N_5O_3S_2$.$1H_2O$ & $0.2CH_2Cl_2$) Calc'd: C, 55.19; H, 4.48; N, 13.30. Found C, 55.14; H, 4.62; N, 12.99.

Example 3(d): 5-{2-[(2S,4R)-4-Hydroxy-2-(1-hydroxy-1-methyl-ethyl)-pyrrolidine-1-carbonyl]-thieno[3,2-*b*]pyridin-7-ylamino}-2-methyl-indole-1-carboxylic acid methylamide



Example 3(d) was prepared in a similar manner to Example 3(a) except that (7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-[(2S,4R)-4-hydroxy-2-(1-hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-methanone, prepared as described below, was used instead of 2-[2-(7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-thiazol-4-yl]-propan-2-ol (0.086 g, 33% yield) as white solid. HPLC: R_t 3.13 min. (100% area). ^{1}H NMR (DMSO-d_6, 300MHz) δ: 8.94 (1H, s), 8.36 (1H, t, J = 2.1Hz), 8.30-8.26 (1H, m), 7.85 (1H, s), 7.67 (1H, d, J = 8.5Hz), 7.43 (1H, s), 7.15 (1H, dd, J = 8.7,1.8), 6.78 (1H, t, J = 4.9Hz), 6.43 (1H, s), 4.76 (1H, s), 3.90-3.78 (2H, m), 2.95 (3H, d, J = 4.2Hz), 2.20 (1H, bs), 1.88-1.72 (2H,m), 1.30 (1H, bs), 1.17 (3H, s), 1.12 (3H, s). HRMS (ESI) $C_{26}H_{29}$ N_5O_4S (M + H^+) *m/z*: Calc. 504.1994, Found 508.2018. Anal. ($C_{26}H_{29}N_5O_4S$•0.2EtOAc) Calc'd: C, 60.90; H, 5.11: N, 13.66. Found: C, 61.25; H, 5.14; N, 13.45.

The starting materials were prepared as follows:

(i) (2S, 4R)-1-(7-Chloro-thieno[3,2-*b*]pyridine-2-carbonyl)-4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester

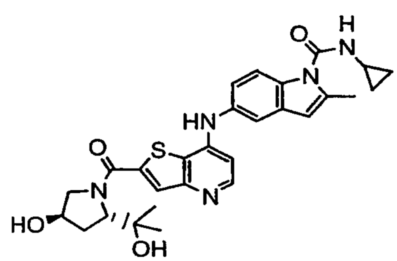
In 10 mL of DMF was added 3.0 g (16.7 mmol) of 7-Chloro-thieno[3,2-*b*]pyridine-2-carboxylic acid lithium salt, 3.20 g (14.66 mmol) of (2S, 4R)-4-Hydroxy-pyrrolidine-2-carboxylic acid methyl ester hydrochloride, PyBop (9.12 g (17.5 mmol) and 5.59 mL (32.1 mmol) of DIEA and the mixture was stirred for 24h. To the mixture was added 50 mL of EtOAc was washed with 50/50 aq. $NaHCO_3$ (2 X 50 mL). The organic layer was dried over Na_2SO_4 and concentrated to give an amber oil. Purification through 100 mL of silica eluting with EtOAc:CH_2Cl_2 (1:1) gave crude product. Diethyl ethyl was used to triturate (2 x 5 mL) the residue to afford 3.43 g (70%) of (2S, 4R)-1-(7-Chloro-thieno[3,2-*b*]pyridine-2-carbonyl)-

4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester as off-white solid. HPLC: R_t 3.36 min. (98.2% area). LCMS (ESI) (M + H$^+$) *m/z*: 341.0.

(ii) (7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-[(2S,4R)-4-hydroxy-2-(1-hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-methanone.

In 5 mL of anhydrous THF was added 0.60 g (1.761 mmol) of (2S, 4R)-1-(7-Chloro-thieno[3,2-*b*]pyridine-2-carbonyl)-4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester then cooled to –78 °C under a Nitrogen atmosphere. To the mixture was then added 1.76 mL (5.28 mmol) of methyl bromo Grignard (3.0 M in THF) drop-wise over 10 min. and the solution was stirred at 0 °C for 3h. The reaction was quenched with 1 mL of $NaHCO_3$ and 50 mL of EtOAc and was washed with 50/50 $NaHCO_3$ (2 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified through silica (30 mL) eluting with EtOAc:CH_2Cl_2:MeOH (7:2:0.1). The uncontaminated fractions were combined and concentrated to give 0.24 g (40%) of (7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-[(2S,4R)-4-hydroxy-2-(1-hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-methanone as a white foam. HPLC: R_t 3.14 min. (98.2% area). LCMS (ESI) (M + H$^+$) *m/z*: 341.1.

Example 3(e): 5-{2-[(2S,4R)-4-Hydroxy-2-(1-hydroxy-1-methyl-ethyl)-pyrrolidine-1-carbonyl]-benzo[b]thiophen-7-ylamino}-2-methyl-indole-1-carboxylic acid cyclopropylamide

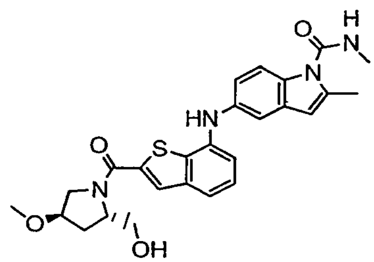


Example 3(e) was prepared in a similar manner to Example 3(d) except that cyclopropylamine was used istead of methylamine (0.042 g, 16% yield). HPLC: R_t 3.35 min. (100% area). ^{1}H NMR (DMSO-d_6, 300MHz) δ: 8.74 (1H, s), 8.38 (1H, t, *J* = 2.1Hz), 8.13 (1H, d, *J* = 5.1Hz), 7.65 (1H, s), 7.40 (1H, d, *J* = 8.8Hz), 7.21 (1H, s), 6.94 (1H, d, *J* = 8.4), 6.56 (1H, d, *J* = 5.3Hz), 6.21 (1H, s), 4.61 (1H, d, *J* = 25.7Hz), 4.27 (1H, t, *J* = 7.9Hz), 4.10 (1H, bs), 3.66-3.47 (2H, m), 2.85 (1H,d, *J* = 3.3Hz), 2.74-2.69 (1H, m), 2.32 (3H, s), 2.01-1.97 (1H, m), 1.63-1.58 (2H, m), 0.96 (3H, s), 0.91 (3H, s), 0.71-0.60 (2H, m), 0.52 (2H, bs). HRMS (ESI) $C_{28}H_{31}N_5O_4S$ (M + H$^+$) *m/z*: Calc. 534.2175, Found 534.2164. Anal.

($C_{28}H_{31}N_5O_4S{\bullet}0.6CH_2Cl_2$) Calc'd: C, 57.86; H, 5.55: N, 11.98. Found: C, 57.71; H, 5.69; N, 11.74.

Example 3(f):5-[2-((2S,4R)-2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carbonyl)-benzo[b]thiophen-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide

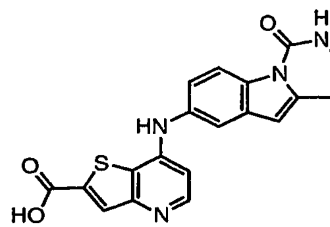
The compound 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic 0.125 g (0.33 mmol), prepared as described below in step (i), was



dissolved in 1 mL of DMF. Added to this reaction mixture was (2S,4R)-4-Methoxy-pyrrolidin-2-yl)-methanol 0.051 g (0.40 mmol), prepared as described below in step (ii)-(iv), PyBop 0.22g (0.43 mmol) and DIEA 0.13 mL (0.73 mmol) and the mixture was stirred for 12h. The solution then was added to 50 mL of EtOAc and was washed with Sat. $NaHCO_3$ (2 X 50 mL). The organic layer was dried over $NaSO_4$ and concentrated. The residue was loaded onto 2-mm Chromatron plate and eluted with EtOAc:CH_2Cl_2:MeOH (1:1:0.1). The purified fractions were concentrated together to give 5-[2-((2S,4R)-2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carbonyl)-benzo[b]thiophen-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide 0.10 g (63%) as yellow powder after precipitating from EtOAc:Hexane (1:1). HPLC: R_t 3.29 min. (100% area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.92 (1H, s), 8.34 (1H, d, J = 5.3Hz), 8.27 (1H, d, J = 4.3Hz), 7.84 (1H, s), 7.69 (1H, d, J = 8.6Hz), 7.43 (1H, s), 7.16 (1H, d, J = 7.3Hz), 6.78 (1H, d, J = 5.3Hz), 6.43 (1H, s), 6.54 (1H, s), 4.88 (1H, t, J = 5.3Hz), 4.28 (1H, bs), 4.09 (1H, q, J = 7.1Hz), 3.97-3.94 (2H, m), 3.78-3.75 (1H, m), 3.58 (1H, bs), 3.23 (3H, s), 2.94 (3H, d, J = 4.3Hz), 2.16-2.10 (2H, m). HRMS (ESI) $C_{25}H_{27}N_5O_4S$ (M + H$^+$) m/z: Calc. 494.1863, Found 494.1876. Anal. ($C_{25}H_{27}N_5O_4S{\bullet}0.2CH_2Cl_2$) Calc'd: C, 59.28; H, 5.41: N, 13.72. Found: C, 59.62; H, 5.46; N, 13.44.

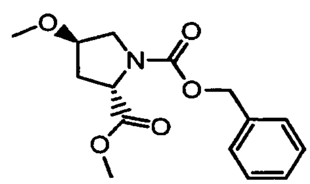
The starting materials were prepared as described below:

(i) 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-*b*]pyridine-2-carboxylic acid



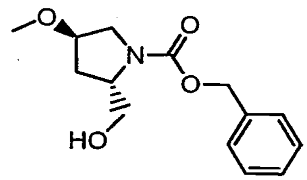
To 0.68 g (1.23 mmol) of 7-Chloro-thieno[3,2-*b*]pyridine-2-carboxylic acid, prepared as described in Groton patent, was added 0.25 g (1.23 mmol) of 5-Amino-2-methyl-indole-1-carboxylic acid methylamide, prepared as described in Example 1(a) steps (i) to (iii), dissolved in 3 mL of DMSO that was degassed with Ar and warmed to 75 °C. The solution was stirred for 14h, cooled to 25 °C and filtered. The precipitate was rinsed with EtOAc (2 x 5 mL) and put under high vacuum for 12h to give 0.43 g (98%) of 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-*b*]pyridine-2-carboxylic acid as yellow solid. HPLC: R_t 3.38 min. (97.2% area). ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.18 (1H, bs), 8.37 (1H, d, J = 5.6 Hz), 8.30 (1H, q, J = 3.4 Hz), 7.94 (1H, s), 7.70 (1H, d, J = 8.7 Hz), 7.46 (1H, s), 7.17 (1H, dd, J = 8.8, 1.9Hz), 6.79 (1H, d, J = 5.6 Hz), 6.45 (1H, s), 2.96 (3H, s), 2.94 (3H, s). LCMS (APCI) (M + H$^+$) m/z: 381.1

(ii) (2S, 4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester



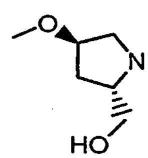
To 2.00 g (7.16 mmol) of (2S, 4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester in 20 mL of acetone was added 5.64g of silver oxide (24.3 mmol) and 1.56 mL of iodomethane (25.0 mmol) and the mixture was stirred at 57°C for 28h. The solution was cooled to 25°C, filtered through celite and concentrated. Purification was through 50 mL of silica by eluting with EtOAc:Hexane (8:1) and the purified fractions were concentrated to give a 2.0g (96%) of (2S,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester as a clear oil. HPLC: R_t 3.79 min. (100% area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 7.31-7.23 (5H, m), 5.22-5.00 (2H, m), 4.44-4.40 (1H, m), 4.10-4.02 (1H, m), 3.76 (3H, s), 3.69-3.60 (1H, m), 3.54 (2H, s), 3.29 (3H, bs), 2.42-2.30 (1H, m). LCMS (ESI) (M + Na$^+$) m/z: 316.1.

(iii) (2S,4R)-2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carboxylic acid benzyl ester



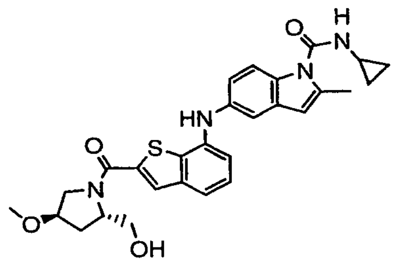
To 5 mL of anhydrous THF was added 1.50 g (5.62 mmol) of (2S, 4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester and the mix was cooled to 0 °C. To reaction mixture was added 3.34 mL of $LiBH_4$ (2.0 M in THF) drop-wise over 5 min and was then stirred for 2 h. The mixture was quenched with 1 mL of Sat. $NaHCO_3$, diluted with 50 mL of EtOAc and washed with Sat. $NaHCO_3$ (2 x 50 mL). The organic layer was dried over $NaSO_4$ and concentrated to give an amber oil. Purification was accomplished through 50 mL of silica eluting with EtOAc/CH_2Cl_2 (7:3). The pure factions were combined, concentrated and subsequently put on the high vacuum for 24h to give 1.3g (92%) of (2S, 4R)-2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carboxylic acid benzyl ester as clear oil. HPLC: R_t 3.41 min. (100% area). ^{1}H NMR ($CDCl_3$, 300MHz) δ; 7.51-7.38 (5H, m), 5.24-5.00 (2H, m), 4.45-4.40 (1H, m), 4.23-4.18 (1H, m), 3.95-3.73 (3H, m), 3.51-3.42 (1H, m), 3.31 (3H, s), 2.22-2.14 (1H, m). LCMS (APCI) (M + H^+) *m/z*: 266.2.

(iv) ((2S,4R)-4-Methoxy-pyrrolidin-2-yl)-methanol



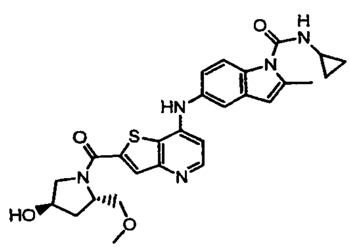
To 1.00 g (5.62 mmol) of (2S, 4R)-2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carboxylic acid benzyl ester in 3 mL of MeOH was added 0.1 g of 10% Pd(C) under 1 atmosphere of H_2 while stirring for 12h. The mixture was filtered through 0.22 μM Teflon filter concentrated and put under high vacuum for 2h to give 0.44 g (96%) of ((2S, 4R)-4-Methoxy-pyrrolidin-2-yl)-methanol as clear oil. LCMS (APCI) (M + H^+) *m/z*: 266.2.

Example 3(g): 5-[2-((2S,4R)-2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carbonyl)-benzo[b]thiophen-7-ylamino]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 3(g) was prepared in a similar manner to Example 3(f) except that cyclopropylamine was used instead of methylamine (0.181 g, 60% yield). HPLC: R_t 3.42 min. (100% area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.94 (1H, s), 8.58 (1H, d, J = 3.0Hz), 8.34 (1H, d, J = 5.3Hz), 7.84 (1H, s), 7.61 (1H, d, J = 8.6Hz), 7.43 (1H, d, J = 1.8), 7.16 (1H, dd, J = 8.8, 2.0Hz), 6.78 (1H, d, J = 5.6Hz), 6.43 (1H, s), 6.54 (1H, s), 4.86 (1H, t, J = 5.5Hz), 4.28 (1H, bs), 4.09 (1H, bs), 3.95-3.89 (2H, m), 3.78-3.75 (1H, m), 3.60-3.58 (1H, m), 3.23 (3H, s), 2.94-2.89 (1H,m), 2.56 (3H, m), 2.15 (2H, t, J = 7.3Hz), 0.84-082 (2H, m), 0.74-071 (2H, m). HRMS (ESI) $C_{27}H_{29}N_5O_4S$ (M + H$^+$) m/z: Calc. 520.2019, Found 520.2020. Anal. ($C_{27}H_{29}N_5O_4S$•0.3EtOAc) Calc'd: C, 62.03; H, 5.80; N, 12.83; S, 5.87. Found: C, 61.80; H, 5.95; N, 13.01; S, 5.87.

Example 3(h): 5-[2-((2S,4R)-4-Hydroxy-2-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]-pyridin-7-ylamino-2-methyl-indole-1-carboxylic acid cyclopropylamide

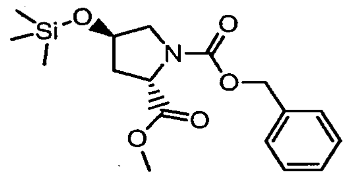


Example 3(h) was prepared in a similar manner to Example 3(f) except that (3R, 5S)-5-Methoxymethyl-pyrrolidin-3-ol, prepared as described below, was used instead of (2S, 4R)-4-Methoxy-pyrrolidin-2-yl)-methanol (0.181 g, 60% yield). HPLC: R_t 3.39 min. (100% area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.92 (1H, s), 8.58 (1H, d, J = 3.0Hz), 8.34 (1H, d, J = 5.5Hz), 7.80 (1H, s), 7.61 (1H, d, J = 8.8Hz), 7.41 (1H,s), 7.15 (1H, dd, J = 8.8), 6.77 (1H, d, J = 5.5Hz), 6.42 (1H, s), 5.03 (1H, s), 4.43-4.38 (2H, m), 3.96 (1H, d, J = 9.6), 3.78-3.74 (1H, m), 3.33 (3H, s), 2.93-2.89 (1H, m), 2.52 (3H, s), 2.07-1.96 (2H, m), 0.83 (2H,d, J = 5.3), 0.73 (2H, d, J = 2.5Hz). HRMS (ESI) $C_{27}H_{29}N_5O_4S$ (M + H$^+$) m/z: Calc. 520.2019, Found

520.2014. Anal. ($C_{27}H_{29}N_5O_4S \bullet 0.3CH_2Cl_2$) Calc'd: C, 60.88; H, 5.52; N, 13.05. Found: C, 61.14; H, 5.55; N, 12.96.

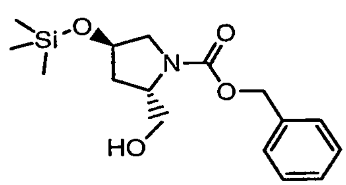
The starting materials were prepared as follows:

(i) (2S, 4R)-4-Trimethylsilanyloxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester



Dissolved (2S, 4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester 1.5 g (5.37 mmol) in 10 mL of THF was treated with DIEA 1.31 mL (7.51 mmol) and 0.89 mL of TMS-Cl (6.98 mmol) added drop-wise while stirring. After 2h of stirring, 50 mL of EtOAc was added and the mix was washed with Sat. $NaHCO_3$ (3 x 50 mL). The organic layer was then dried over Na_2SO_4, filter through silica and concentrated to afford 1.84 g (97%) of (2S, 4R)-4-Trimethylsilanyloxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester as a clear oil. HPLC: R_t 4.12 min. (100% area). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.28 (5H, m), 5.22-5.01 (2H, m), 4.51-4.41 (2H, m), 3.76 (2H, s), 3.70-3.66 (1H, m), 3.51-3.39 (1H, m), 2.22-2.16 (1H, m), 2.04 (3H, s), 0.11 (9H, s).

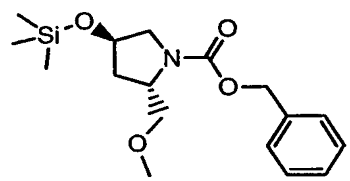
(ii) (2S, 4R)-2-Hydroxymethyl-4-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester



To (2S, 4R)-4-Trimethylsilanyloxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester 1.50 g (4.22 mmol) in 5 mL of anhydrous THF under an atmosphere of Ar in an ice bath, was added 2.56 mL $LiBH_4$ (2.0 M in THF, 5.12 mmol) drop-wise. The solution was stirred for 3h. The mixture was quenched with 1 mL of Sat. $NaHCO_3$ and EtOAc (50 mL). The organics were washed with Sat. $NaHCO_3$ (2 x 50 mL). The organic layer was dried over Na_2SO_4 and the solution was concentrated to afford 1.31 g (96%) of (2S, 4R)-2-Hydroxymethyl-4-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester as clear oil. HPLC: R_t 2.87 min. (100% area). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.20 (5H, m), 5.05 (2H, s), 4.47 (1H, d, J = 7.4 Hz), 4.20 (1H, bs), 4.08 (1H, q, J = 7.3 Hz), 3.64 (1H, t , J = 9.1 Hz),

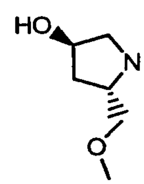
3.51-3.47 (1H, m), 3.41-3.35 (2H, m), 1.89-1.84 (1H, m), 1.57-1.52 (1H, m), 0.11 (9H, s). LCMS (ESI) (M + H^+) *m/z*: 324.2.

(iii) (2S, 4R)-2-Methoxymethyl-4-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester



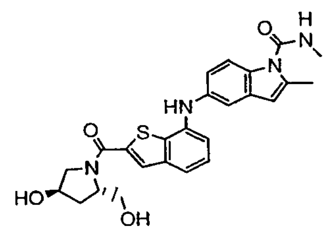
To (2S, 4R)-2-Hydroxymethyl-4-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester in 10 mL of acetone was added iodomethane 0.86 mL (13.5 mmol), silver oxide 3.04 g (13.2 mmol) and the solution was warmed to 57°C for 8h. The mixture was cooled to 25°C, filtered through celite and concentrated. The residue was taken up in 50 mL of EtOAc and was washed with Sat. $NaHCO_3$ (2 x 50 mL). The organic layer dried over Na_2SO_4 and concentrated. The residue was loaded onto 50 mL silica and eluted with Hexane:EtOAc (3:7). The purified fraction were concentrated to give 0.66 g (67%) of (2S, 4R)-2-Methoxymethyl-4-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester as clear oil. HPLC: R_t 3.43 min. (98.2% area). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.38-7.32 (5H, m), 4.70 (2H, s), 4.56-4.46 (2H, m), 4.18-4.13 (2H, m), 3.86 (1H, q , J = 5.5 Hz), 3.07-3.02 (1H, m), 1.99-1.95 (1H, m), 1.61 (3H, bs), 1.57-1.52 (1H, m), 0.12 (9H, s). LCMS (ESI) (M + H^+) *m/z*: 338.2.

(iv) (3R, 5S)-5-Methoxymethyl-pyrrolidin-3-ol



To (2S, 4R)-2-Methoxymethyl-4-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester 1.00 g (3.98 mmol) in 3 mL of methanol was added 10% Pd(C) 0.10g and the mixture was stirred under 1 atmosphere of hydrogen for 24h. The mixture was filtered through a 0.22 μM Teflon filter, concentrated and subsequently put on a high vacuum for 2h to afford 0.43g (86%) of (3R, 5S)-5-Methoxymethyl-pyrrolidin-3-ol as clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.30 (1H, s), 4.67 (1H, t, J = 5.6 Hz), 4.56 (1H, t, J = 7.6 Hz), 4.26-4.21 (1H, m), 4.19 (1H, dd, J = 8.1, 3.3 Hz), 3.14 (1H, d, J = 12.3 Hz), 2.08 (1H, dd, J = 8.2, 3.2 Hz), 1.66-1.59 (3H, m). LCMS (ACPI) (M + H^+) *m/z*: 132.2.

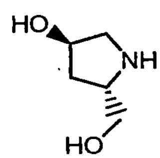
Example 3(i): 5-[2-((2S, 4R)-4-Hydroxy-2-hydroxymethyl-pyrrolidine-1-carbonyl)-benzo[b]thiophen-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



Example 3(f) was prepared in a similar manner to Example 3(d) except that (2S, 4R)-4-hydroxy-2-hydroxymethyl-pyrrolidine, prepared as described below, was used instead of (2S, 4R)-4-Methoxy-pyrrolidin-2-yl)-methanol (0.23 g, 59% yield). HPLC: R_t 3.77. (95% area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.71 (1H, s), 8.10 (1H, d, J = 4.8Hz), 8.05 (1H, d, J = 3.8Hz), 7.55 (1H, s), 7.44 (1H, d, J = 8.6Hz), 7.19 (1H, s), 6.92 (1H, d, J = 8.1), 6.54 (1H, d, J = 5.3 Hz), 6.19 (1H, s), 4.75 (1H, s), 4.59 (1H, bs) 4.16-4.05 (2H, m), 3.69 (1H, d, J = 7.9), 3.55-3.45 (2H, m), 3.36 (1H, bs), 3.23-3.19 (1H, m), 3.15 (3H, s), 2.70 (3H, d, J = 3.8Hz), 1.91-1.85 (1H, m), 1.73 (1H, t, J = 6.2Hz), 0.91 (1H, t, J = 6.8Hz). HRMS (ESI) $C_{24}H_{25}N_5O_4S$ (M + H^+) *m/z*: Calc'd: 480.1706, Found: 480.1713. Anal. ($C_{24}H_{25}N_5O_4S$•$1.1H_2O$) Calc'd: C, 57.72; H, 5.49: N, 14.03. Found: C, 57.64; H, 5.27; N, 13.84.

The starting material was prepared as follows:

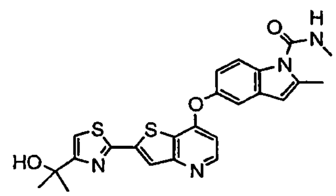
(i) (3R, 5S)-5-Hydroxymethyl-pyrrolidin-3-ol



To (2S, 4R)-2-Methoxymethyl-4-trimethylsilanyloxy-pyrrolidine-1-carboxylic acid benzyl ester (1.00g, 3.98 mmol), prepared in Example 3(h) step (ii), in 3 mL of methanol was added 10% Pd(C) 0.10g under 1 atmosphere of hydrogen. The mix was stirred for 24h. The mixture was filtered through 0.22 μM Teflon filter concentrated and subsequently placed under a high vacuum for 4h to afford 0.45g (97%) of (3R, 5S)-5-Hydroxymethyl-pyrrolidin-3-ol as clear oil. LCMS (ACPI) (M + H^+) *m/z*: 118.1.

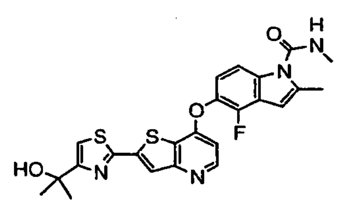
Example 3(j): 5-{2-[4-(1-Hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*]pyridin-7-yloxy}-2-methyl-3a,7a-dihydro-indole-1-carboxylic acid methylamide.

Example 3(j) was prepared by combining (0.10 g, 0.24 mmol) of 2-{2-[7-(2-Methyl-1H-



indol-5-yloxy)-benzo[b]thiophen-2-yl]-thiazol-5-yl}-propan-2-ol dissolved in 3 ml CH_2Cl_2, NaOH (0.28g, 0.72), TABBr (0.01g, 0.024 mmol) and methylisocynate (0.04g, 0.72 mmol) and stirring for 1h. Partitioned the reaction mixture with 50/50 $NaHCO_3$ (2 x 50 mL) then concentrated. Purification was through a 2 mm C-tron silica plate eluting with EtOAc/CH_2Cl_2/MeOH (7:3:0.1) combined purified fraction afforded 5-{2-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-b]pyridin-7-yloxy}-2-methyl-3a,7a-dihydro-indole-1-carboxylic acid methylamide (0.07g, 62%) as white solid. HPLC: R_t 4.10 min. (100% area). ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.42 (1H, d, J = 5.3 Hz), 7.86 (1H, s), 7.72 (1H, d, J = 8.8 Hz), 7.29 (1H, s), 7.20 (1H, s), 7.02 (1H, d, J = 6.3 Hz), 6.51 (1H, d, J = 6.3 Hz), 6.32 (1H, s), 5.82 (1H, bs), 3.21 (3H, s), 2.60 (3H, s), 1.66 (6H, s). HRMS (ESI) $C_{24}H_{23}N_4O_3S_2$ (M + H$^+$) *m/z*: Calc. 479.1205, Found: 479.1207. Anal. ($C_{24}H_{23}N_4O_3S_2$•$0.3CH_2Cl_2$) Calc'd: C, 57.90; H, 4.52; N, 11.22. Found: C, 57. 53; H, 4.52; N, 11.22.

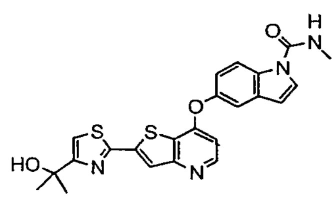
Example 3(k): 4-Fluoro-5-{2-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-b]pyridin-7-yloxy}-2-methyl-indole-1-carboxylic acid methylamide.



Example 3(k) was prepared in a similar manner to Example 3(j) except that 2-{2-[7-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-benzo[b]thiophen-2-yl]-thiazol-5-yl}-propan-2-ol was used instead. After purification, 4-Fluoro-5-{2-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-b]pyridin-7-yloxy}-2-methyl-indole-1-carboxylic acid methylamide (0.098 g, 59% yield) was afforded as a white solid. HPLC: R_t 4.27 min. (95 % area). ^{1}H NMR ($CDCl_3$,

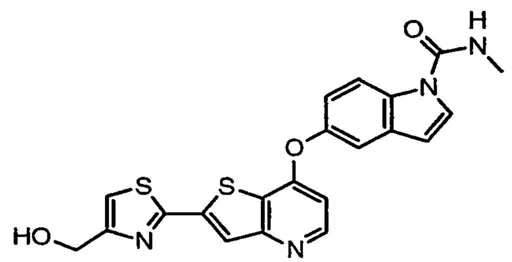
400MHz) δ: 8.46 (1H, d, J = 5.6 Hz), 7.90 (1H, s), 7.50 (1H, d, J = 8.9 Hz), 7.20 (1H, s), 7.11 (1H, t, J = 5.1 Hz), 6.48 (1H, bs), 5.66 (1H, bs), 3.14 (3H, s), 2.62 (3H, s), 1.67 (3H, s), 1.58 (3H, s). HRMS (ESI) $C_{24}H_{22}FN_4O_3S_2$ (M + H^+) *m/z*: Calc. 497.1116, Found: 497.1101. Anal. ($C_{24}H_{22}FN_4O_3S_2$•0.2 Hex) Calc'd: C, 58.90; H, 4.67; N, 10.90. Found: C, 58.88; H, 4.66; N, 10.73.

Example 3(l): 5-{2-[4-(1-Hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*]pyridin-7-yloxy}-indole-1-carboxylic acid methylamide



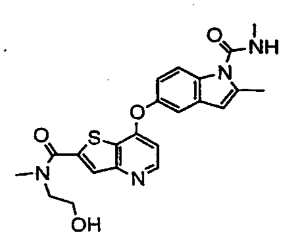
Example 3(l) was prepared in similar manner as 3(j) except that the starting material 2-{2-[7-(1H-Indol-5-yloxy)-benzo[b]thiophen-2-yl]-thiazol-5-yl}-propan-2-ol (0.100 g, 0.234 mmol) was used instead. After titration with Hex/CH_2Cl_2 (1:1) to purify afforded the product 5-{2-[4-(1-Hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*]pyridin-7-yloxy}-indole-1-carboxylic acid methylamide (0.56, 51.0%) as a white solid. HPLC: R_t 4.07 min. (94 % area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.47 (2H, t, J = 5.4 Hz), 8.25 (1H, d, J = 9.1 Hz), 7.89 (1H, bs), 7.49-7.41 (2H, m), 7.21-7.17 (1H, m), 6.66 (1H, d, J = 16.7 Hz), 6.55 (1H, t, J = 6.4 Hz), 5.62 (1H, bs), 3.10 (3H, d, J = 4.6 Hz), 2.96 (3H, d, J = 6.5 Hz), 2.75 (3H, s). HRMS (ESI) $C_{23}H_{21}N_4O_3S_2$ (M + H^+) *m/z*: Calc. 465.1047; Found: 465.1047. Anal. ($C_{23}H_{20}N_4O_3S_2$•0.6 H_2O) Calc'd: C, 58.11; H, 4.50; N, 11.79. Found: C, 58.47; H, 4.94; N, 10.12.08.

Example 3(m): 5-[2-(4-Hydroxymethyl-thiazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-indole-1-carboxylic acid methylamide



Example 3(m) was prepared in a similar manner to Example 3(j) except that the starting material [2-(7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-thiazol-4-yl]-methanol, prepared in example 27 of section A of PC10795A, was used instead of [2-(7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-thiazol-4-yl]-propan-2-ol. Elution with EtOAc:CH_2Cl_2:MeOH (1:1:0.1) through a flash column and subsequent concentration provided the product as a yellow solid (0.12 g, 56% yield). HPLC: R_t 3.73 min. (100 % area). ^{1}H NMR (MeOD, 400MHz) δ: 8.34 (1H, d, J = 5.6 Hz), 7.84 (1H, s), 7.63 (1H, d, J = 8.9 Hz), 7.45 (1H, s), 7.25 (1H, t, J = 2.2 Hz), 6.97 (1H, dd, J = 5.6, 2.5), 6.55 (1H, d, J = 5.6 Hz), 6.26 (1H, s), 4.66 (2H, s), 2.62 (3H, s), 2.46 (3H, s). HRMS $C_{22}H_{19}N_4O_3S_2$ (ESI) (M + H^+) *m/z*: Calc. 451.0899, Found: 451.0921. Anal. ($C_{22}H_{19}N_4O_3S_2$•0.2 CH_2Cl_2) Calc'd: C, 57.03; H, 3.97; N, 11.98. Found: C, 57.19; H, 3.95; N, 11.98.

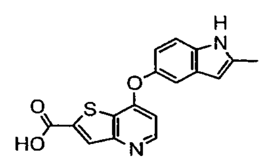
Example 3(n): 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid (2-hydroxy-ethyl)-methyl-amide.



To a solution of DMF was added 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid (.1g, .26 mmol), as prepared in step (iv), 2-Methylamino-ethanol (0.025 mL, 0.35 mmol) as well as HATU (0.12g, .32) and DIEA (0.051 mL, 0.32 mmol) then stirred for 3h. To the solution was added 30 mL of EtOAc portioned between 50/50 $NaHCO_3$ (2 x 30 mL) and the organic layer dried over Na_2SO_4 then concentrated via rotor evaporator. The title compound was purified with flash chromatography eluting with EtOAc/CH_2Cl_2/MeOH (2:1:0.1) and the purified fraction

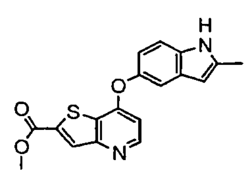
concentrate to afford 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid (2-hydroxy-ethyl)-methyl-amide as an off-white solid (0.041 g, 36%). . HPLC: R_t 3.35 min. (96 % area). ^{1}H NMR (DMSO-d$_3$, 400MHz) δ: 8.46 (1H, d, J = 4.3 Hz), 8.22 (1H,bs), 7.90-7.81 (1H, m), 7.61 (1H, d, J = 8.6 Hz), 7.34 (1H, s), 7.01 (1H, dd, J = 8.6, 2.3 Hz), 6.57 (1H, d, J = 5.5 Hz), 6.33 (1H, s), 3.56 (5H, m), 2.96 (2H, bs), 2.81 (3H, d, J = 5.5 Hz), 2.43 (3H, s). LCMS (ACPI) M + H$^+$ *m/z*: 439.1. Anal. ($C_{22}H_{22}N_4O_4S$•1.0 H_2O •0.3 EtOAc) Calc'd: C, 57.60; H, 5.07; N, 11.63. Found: C, 57.87; H, 4.93; N, 11.25.

Step (i) 7-(2-Methyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid.



Method A: To a solution of 3 mL of DMSO was added 7-Chloro-thieno[3,2-*b*]pyridine-2-carboxylic acid (0.6g, 2.63 mmol), 2-Methyl-3a,7a-dihydro-1H-indol-5-ol (0.42g, 2.63 mmol), MeOH (0.5 mL) and Cs_2CO_3 (1.7g, 5.35 mmol) then sealed and warmed to 165 °C for 3h and cooled to 25 °C. To the reaction solution was added 50 mL of EtOAc then portioned between 50/50 $NaHCO_3$ (50 mL). The aqueous layer was then acidified using concentrated HCl drop wise to afford 7-(2-Methyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid (0.65 g, 76 %) as a white solid. HPLC: R_t 3.62 min. (92 % area). ^{1}H NMR (DMSO-d$_3$, 400MHz) δ: 11.07 (1H, s), 8.45 (1H, d, J = 5.3 Hz), 7.98 (1H, s), 7.23 (1H, d, J = 8.9 Hz), 7.19 (1H, d, J = 7.5, 3.4 Hz), 6.78 (1H, dd, J = 6.3, 2.3 Hz) 6.57 (1H, d, J = 5.5 Hz), 6.03 (1H, s), 2.26 (3H, s). LCMS (ACPI) M + H$^+$ *m/z*: 325.

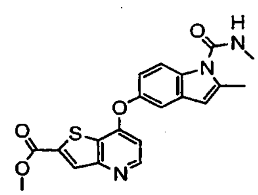
Step (ii) 7-(2-Methyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid methyl ester.



To a solution of DMF was added 7-(2-Methyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid (0.6 g, 1.85 mmol), DIEA (0.62 mL, 3.70 mmol), HATU (0.77 g, 2.03)

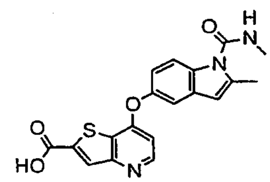
and MeOH (0.5 mL). The solution was stirred for 3h then 50 mL of EtOAc added and partitioned between 50/50 $NaHCO_3$ (2 x 50 mL). The organic layer was dried over Na_2SO_4 then concentrated. Purification was through silica (50 mL) eluting with EtOAc/Hex (2:1). The purified fraction combined and concentrated to give 7-(2-Methyl-1H-indol-5-yloxy)-thieno[3,2-b]pyridine-2-carboxylic acid methyl ester as white foam (0.6g, 96%). HPLC: R_t 4.01 min. (100% area). ^1H NMR ($CDCl_3$-d_3, 400MHz) δ: 8.42 (1H, d, J = 5.6 Hz), 8.29 (1H, bs), 7.26-7.23 (2H, m), 6.85 (1H, dd, J = 7.5, 1.6 Hz), 6.51 (1H, d, J = 5.3 Hz), 6.17 (1H, s), 3.91 (3H, s), 2.40 (3H, s). LCMS (ACPI) M + H^+ *m/z*: 339.1.

Step (iii): 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*] pyridine-2-carboxylic acid methyl ester.



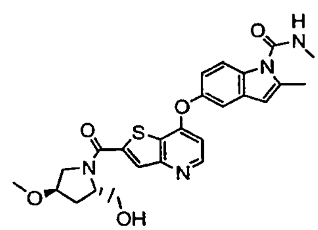
To a solution of methlyene chloride (2 mL) was added 7-(2-Methyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid methyl ester (0.4g, 1.82 mmol), DBU (0.5 mL, 3.5 mmol), 4-nitrophenyl chloroformate (0.72g, 3.5 mmol) then stirred at 0°C for 24h. Next was added 2.4 mL of methyl amine (2.0 M in THF) via syringe and stirred an addition 1h. To the reaction mixture was added 50 mL of EtOAc worked-up by portioning between 50/50 $NaHCO_3$ and concentrated. Purification was through silica (30 mL) eluting with EtOAc/CH_2Cl_2/MeOH (2:1:0.1) combined purified fraction to afford 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid methyl ester as yellow solid (0.35 g, 74 %). HPLC: R_t 3.96 min. (100% area). ^1H NMR ($CDCl_3$-d_3, 400MHz) δ: 8.40 (1H, d, J = 5.6 Hz), 8.09 (1H, s), 7.64 (1H, d, J = 8.8 Hz), 6.92 (1H, dd, J = 7.4, 2.2 Hz), 6.84 (1H, d, J = 9.1 Hz), 6.49 (1H, d, J = 5.3 Hz), 6.23 (1H, s), 5.98 (1H, d, J = 4.5 Hz), 3.89 (3H, s), 3.04 (3H, d, 4.5 Hz), 2.52 (3H, s). LCMS (ACPI) M + H^+ *m/z*: 396.2.

Step (iv): 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*] pyridine-2-carboxylic acid.



A solution of THF (5 mL), MeOH (1 mL) and H_2O (1 mL) was used to dissolve LiOH·H_2O (0.042 g, 1.0 mmol) and then added 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid methyl ester (0.35 g, 0.89 mmol) added. The solution was stirred at 25 °C for 2h, quenched with several drops of 1N HCl then concentrated. The precipitate was rinsed with H_2O (2 x 5 mL) and Et_2O (2 x 5 mL), dried under high vacuum for 2h and used as is to afford 7-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[3,2-*b*]pyridine-2-carboxylic acid (0.25g, 73%) as yellow solid. HPLC: R_t 3.43 min. (95% area). LCMS (ACPI) M + H^+ *m/z*: 382.1.

Example 3(o): 5-[2-(2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide.

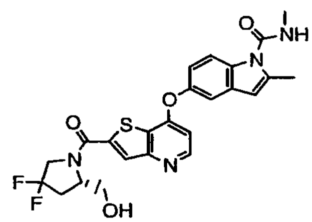


Example 3(o) was prepared by dissolving the starting material 5-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-methoxy-pyrrolidine-1-carbonyl]-thieno[3,2-*b*]pyridin-7-yloxy}-2-methyl-indole-1-carboxylic acid methylamide (0.55 g, 1.00 mmol), as prepared in step i below, in 1 mL of acetic acid in 0.5 mL of THF and 0.5 mL of TFA and stirring at 50°C for 3h. The reaction mixture was quenched with 5 mL of sat. $NaHCO_3$ and 50 mL of EtOAc the partitioned with 50/50 $NaHCO_3$ (2 x 50 mL) organic layer dried over $NaSO_4$ and concentrated. The residue purified with a 2 mm choromatotron rotor eluting with EtOAc/CH_2Cl_2/MeOH (2:1:0.2) then combining purified fractions. The product was

then crashing out of EtOAc and diethyl ether producing 0.34 g (68.5 %) of 5-[2-(2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide as white solid. HPLC: R_t 5.06 min. (94 % area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.50 (1H, d, J = 5.3 Hz), 7.81 (1H, s), 7.71 (1H, d, J = 9.0), 7.30 (1H, s), 7.03 (1H, d, J = 6.9 Hz), 6.60 (1H, d, J = 5.3 Hz), 6.33 (1H, s), 5.69 (1H, bs), 4.57 (1H, q, J = 6.8 Hz), 4.33 (1H, s), 4.08 (1H, d, J = 11.6 Hz), 4.00 (1H, s), 3.86 (2H, t, J = 11.6 Hz), 3.85-3.75 (1H, m), 3.28 (3H, d, J = 4.3 Hz), 2.61 (3H, s), 2.34-2.29 (1H, m). HRMS (ESI) $C_{25}H_{27}N_4O_5S_2$ (M + H$^+$) *m/z*: Calc. 495.1702, Found: 495.1704. Anal. ($C_{25}H_{26}N_4O_5S_2$•0.2 EtOAc) Calc'd: C, 60.50; H, 5.43; N, 10.94; Found: C, 60.73; H, 5.61; N, 10.10.86.

Example 3(p): 5-[2-(4,4-Difluoro-2-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methyl-amide.

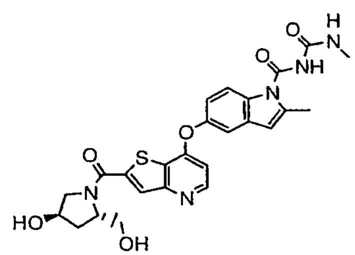
Example 3(p) was prepared in a similar manne: to Example 3(n) except that 5-{2-[2-(tert-



Butyl-dimethyl-silanyloxymethyl)-4,4-difluoro-pyrrolidine-1-carbonyl]-thieno[3,2-*b*]pyridin-7-yloxy}-2-methyl-indole-1-carboxylic acid methylamide was used instead of 5-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-methoxy-pyrrolidine-1-carbonyl]-thieno[3,2-b]pyridin-7-yloxy}-2-methyl-indole-1-carboxylic acid methylamide. The title compound was purified with flash chromatography eluting with EtOAc/CH_2Cl_2/IPA (3:1:0.2) and the purified fraction concentrate to afford an off-white solid (0.066 g, 74%) of 5-[2-(4,4-Difluoro-2-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide. HPLC: R_t 3.51 min. (100% area). ^{1}H NMR (CDCl- 400MHz) δ: 8.49 (1H, d, J = 5.6 Hz), 7.81 (1H, s), 7.63 (1H, d, J = 8.8 Hz), 7.25 (1H, = 2.2 Hz), 6.65 (1H, dd, J = 6.9, 2.2 Hz), 6.60 (1H, d, J = 5.6 Hz), 6.30 (1H, s), 4.55 (1H, bs), 4.22-4.16 (2H, m), 3.90-3.75 (1H, m), 3.62-3.50 (1H, bs), 2.92 (3H, s), 2.60-2.51 (2H, m), 2.46 (3H,s). HRMS (ESI) $C_{25}H_{23}N_4O_4S$ (M + H$^+$)

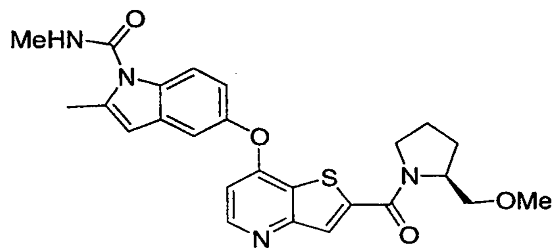
m/z: Calc. 501.1420, Found: 501.1425. Anal. ($C_{25}H_{23}N_4O_4S$•3.2 H_2O) Calc'd: C, 51.64; H, 5.13; N, 10.04. Found: C, 51.42; H, 5.13; N, 10.04.

Example 3(q): 1-{5-[2-(4-Hydroxy-2-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carbonyl}-3-methyl-urea.



The starting material 1-{5-[2-(2-Hydroxymethyl-4-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carbonyl}-3-methylurea (0.056g, 0.11 mmol) was dissolved in 5 mL of anhydrous methylene chloride and cooled to 0 °C. To reactrion mixture was the addition of BBr_3 (2.5 M in CH_2Cl_2, 0.16 mL, 0.40 mmol) drop-wise via airtight syringe under a nitrogen atmosphere. The reaction was quenched with 2 mL of Sat. $NaHCO_3$ and 20 mL of CH_2Cl_2 and partitioned between 50/50 $NaHCO_3$ (2 x 20 mL) and the organic layer dried over and concentrated. The residue was purified using a 2 mm chromatotron rotor eluting with EtOAc/CH_2Cl_2/MeOH (1:1:0.2) and the purified fraction concentrated. The purified residue was then added to 5 mL of 1:1 mixture of CH_2Cl_2/Hexane that afforded 0.025 g (48%) of 5-[2-(4-Hydroxy-2-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide as a white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 8.63 (1H, d, J = 5.3 Hz), 8.06 (1H, d, J = 4.6 Hz), 8.00 (1H, s), 7.60 (1H, d, J = 9.1), 7.17 (1H, dd, J = 8.9, 2.3 Hz), 6.74 (1H, s), 6.54 (1H, s), 5.02 (1H, s), 4.85 (1H, bs), 4.40-4.35 (2H, m), 3.98-3.90 (1H, m), 3.80-3.71 (2H, m), 3.60-3.53 (1H, m), 2.16-2.97 (2H, m). LCMS (ACPI) (M + H$^+$) *m/z*: 524.1. Anal. ($C_{25}H_{25}N_5O_6S$•0.8 EtOAc•1.5 H_2O) Calc'd: C, 54.55; H, 5.58; N, 11.28. Found: C, 54.49; H, 5.27; N, 10.96.

Example 4(a): 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-*b*]pyridin-7-yloxy)-2-methylindole-1-carboxylic acid methylamide



This material was prepared by the treatment of 2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1-(4-nitrophenoxy)indole (60 mg, 0.1 mmole) with methylamine in a manner as previously described for Example 1(a), step (ii) to give 40 mg (82%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.54 (1H, d, J = 5.4 Hz), 8.27 (1H, q, J= 4.5 Hz), 8.00 (1H, s), 7.68 (1H, d, J = 9.0 Hz), 7.40 (1H, d, J = 2.4 Hz), 7.07 (1H, dd, J = 2.4, 9.0 Hz), 6.65 (1H, d, J = 5.4 Hz), 6.40 (1H, s), 4.36-4.25 (1H, m), 3.93-3.76 (2H, m), 3.59-3.38 (2H, m), 3.27 (3H, s), 2.88 (3H, d, J = 4.5 Hz), 2.48 (3H, s), 2.06-1.83 (4H, m). *Anal.* Calcd. for $C_{25}H_{26}N_4O_4S \bullet 0.25\ H_2O$:: C, 62.16; H, 5.53; N, 11.60. Found: C, 62.12; H, 5.49; N, 11.27.

The starting materials were prepared as follows:

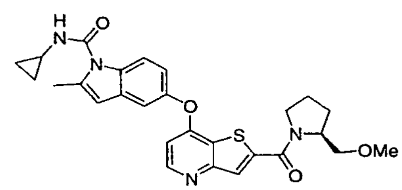
(i) **7-chloro-2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine** The title compound was prepared in a similar manner to (7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-(2R-hydroxymethyl-pyrrolidin-1-yl)-methanone, except that 2S-methoxymethyl-pyrrolidine was used instead of 2R-hydroxymethyl-pyrrolidine.

(ii) 2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)indole. A solution of 7-chloro-2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine (1.55 g, 5 mmol), and 5-hydroxy-2-methylindole (1.18 g, 8 mmole) in DMSO (40 ml) was purged with argon for minutes at ambient temperature prior to addition of freshly crushed Cs_2CO_3 (4.88 g, 15 mmol). The resultant reaction mixture was heated at 105°C for 2 hours. After cooling to room temperature, the crude reaction mixture was poured into cold water (300 ml). The precipitate that formed was collected by filtration to give 2.4 g of a brown solid which was purified by silica gel chromatography. Elution with CH_2Cl_2: CH_3OH (96:4) and evaporation of the appropriate fractions gave 1.61g (77%) of a yellow solid. ^{1}H NMR (DMSO-d6): δ 11.14 (1H, s), 8.51 (1H, d, J = 5.4 Hz), 7.98 (1H, s),

7.35 (1H, d, J = 8.6 Hz), 7.29 (1H, d, J = 2.3 Hz), 6.88 (1H, dd, J = 2.3, 8.6 Hz), 6.62 (1H, d, J = 5.4 Hz), 6.16 (1H, s), 4.36-4.25 (1H, m), 3.93-3.75 (2H, m), 3.59-3.49 (1H, m), 3.46-3.36 (1H, m), 3.27 (3H, s), 2.39 (3H, s), 2.06-1.83 (4H, m).

(iii) 2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1-(4-nitrophenoxy)indole. This material was prepared by the acylation of 2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)indole (1.1 g, 2.6 mmole) with 4-nitrophenyl chloroformate (1.8 g, 8.9 mmole) as previously described for Example 1(a), step (i), Method B, to provide 742 mg (48%) of a yellow solid. ^{1}H NMR (DMSO-d6): δ 8.57 (1H, d, J = 5.4 Hz), 8.40 (2H, d, J = 9.0 Hz), 8.18 (1H, d, J = 8.9 Hz), 8.01 (1H, s), 7.80 (2H, d, J = 9.0 Hz), 7.51 (1H, d, J = 2.3 Hz), 7.23 (1H, dd, J = 2.3, 8.6 Hz), 6.73 (1H, d, J = 5.4 Hz), 6.66 (1H, s), 4.36-4.23 (1H, m), 3.93-3.75 (2H, m), 3.59-3.37 (2H, m), 3.27 (3H, s), 2.68 (3H, s), 2.05-1.81 (4H, m).

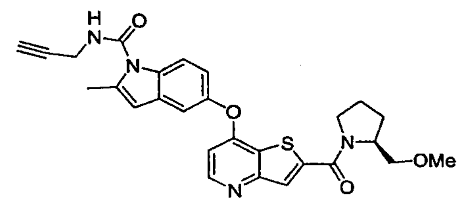
Example 4(b): 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylindole-1-carboxylic acid cyclopropylamide.



Example 4(b) was prepared in a similar manner as Example 4(a) except that cyclopropylamine was used instead of methylamine to give 355 mg (69%) of a yellow solid. ^{1}H NMR (DMSO-d6): δ 8.56 (1H, d, J= 3.4 Hz), 8.54 (1H, d, J = 5.4 Hz), 8.00 (1H, s), 7.60 (1H, d, J = 8.8 Hz), 7.39 (1H, d, J = 2.3 Hz), 7.06 (1H, dd, J = 2.3, 8.8 Hz), 6.64 (1H, d, J = 5.4 Hz), 6.39 (1H, s), 4.36-4.25 (1H, m), 3.94-3.75 (2H, m), 3.59-3.38 (2H, m), 3.27 (3H, s), 2.91-2.78 (1H, m), 2.48 (3H, s), 2.06-1.83 (4H, m), 0.82-0.61 (4H, m). *Anal.* Calcd. for $C_{27}H_{28}N_4O_4S$•0.5 H_2O: C, 63.14; H, 5.69; N, 10.91. Found: C, 63.14; H, 5.62; N, 10.65.

Example 4(c): 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylindole-1-carboxylic acid prop-2-ynylamide

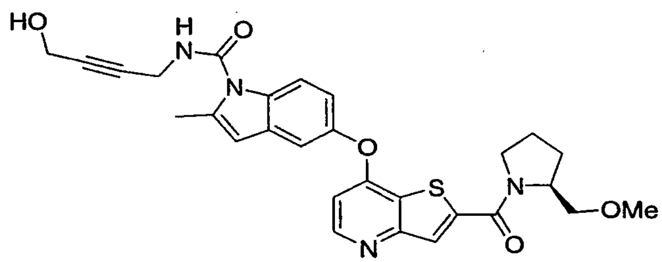
Example 4(c) was prepared in a similar manner as Example 4(a) except that



propargylamine was used instead of methylamine to give 55 mg (71%) of a yellow solid. ^{1}H NMR (DMSO-d6): δ 8.84 (1H, t, J= 5.7 Hz), 8.53 (1H, d, J = 5.4 Hz), 8.00 (1H, s), 7.69 (1H, d, J = 8.8 Hz), 7.41 (1H, d, J = 2.3 Hz), 7.10 (1H, dd, J = 2.3, 8.8 Hz), 6.65 (1H, d, J = 5.4 Hz), 6.42 (1H, s), 4.36-4.25 (1H, m), 4.11 (2H, dd, J = 2.2, 5.7 Hz), 3.93-3.75 (2H, m), 3.59-3.38 (2H, m), 3.27 (3H, s), 2.48 (3H, s), 2.05-1.79 (5H, m). *Anal.* Calcd. for $C_{27}H_{26}N_4O_4S$: C, 64.52; H, 5.21; N, 11.15. Found: C, 64.21; H, 5.25; N, 11.00.

Example 4(d): 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylindole-1-carboxylic acid (4-hydroxybut-2-ynyl)amide.

A solution of 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-



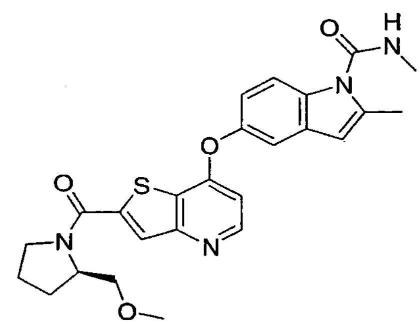
b]pyridin-7-yloxy)-2-methylindole-1-carboxylic acid [4-(t-butyldimethylsilyloxy)but-2-ynyl]amide (60 mg, 0.1 mmole), prepared as described below, in THF (5 ml) was treated with 2 M nBu_4NF in THF (0.2 ml). The reaction mixture was stirred at ambient temperature for 1 hour, then diluted with water (5 ml) and extracted with EtOAc (3 x 15 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, *in vacuo*, to give an amber resin, which was purified by silica gel chromatography. Elution with CH_2Cl_2: CH_3OH (95:5) and evaporation of the appropriate fractions gave 46 mg (94%) of a amber solid. ^{1}H NMR (DMSO-d6): δ 8.83 (1H, t, J= 5.7 Hz), 8.54 (1H, d, J = 5.4 Hz), 8.00 (1H, s), 7.68 (1H, d, J = 8.8 Hz), 7.40 (1H, d, J = 2.2 Hz), 7.08 (1H, dd, J = 2.2, 8.8 Hz), 6.64 (1H, d, J = 5.4 Hz), 6.41 (1H, s), 4.38-4.24 (3H, m), 4.14 (2H, d, J = 5.7 Hz), 3.93-3.76 (2H, m), 3.58-3.38 (2H, m), 3.27 (3H, s), 2.48 (3H, s), 2.04-1.82 (4H, m). *Anal.* Calcd. for $C_{28}H_{28}N_4O_5S{\bullet}0.5$ toluene: C, 65.38; H, 5.57; N, 9.68. Found: C, 65.39; H, 5.60; N, 9.44.

The starting material was prepared as follows:

(i) 5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylindole-1-carboxylic acid [4-(t-butyldimethylsilyloxy)but-2-ynyl]amide.

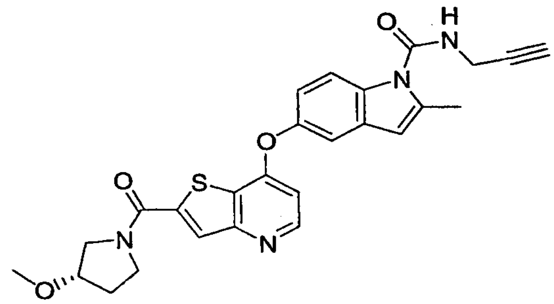
The title compound was prepared in a similar manner as Example 4(a) except that 4-(t-butyldimethylsilyloxy)but-2-ynylamine was used instead of methylamine to give 65 mg (66%) of a yellow solid. ^{1}H NMR (DMSO-d6): δ 8.82 (1H, t, J= 5.7 Hz), 8.54 (1H, d, J = 5.4 Hz), 8.00 (1H, s), 7.69 (1H, d, J = 8.8 Hz), 7.41 (1H, d, J = 2.1 Hz), 7.07 (1H, dd, J = 2.1, 8.8 Hz), 6.66 (1H, d, J = 5.4 Hz), 6.42 (1H, s), 4.37-4.25 (3H, m), 4.16 (2H, d, J = 5.7 Hz), 3.92-3.76 (2H, m), 3.56-3.37 (2H, m), 3.27 (3H, s), 2.48 (3H, s), 2.04-1.83 (4H, m), 0.85 (9H, s), 0.09 (6H, s).

Example 4(e): 5-[2-(2R-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



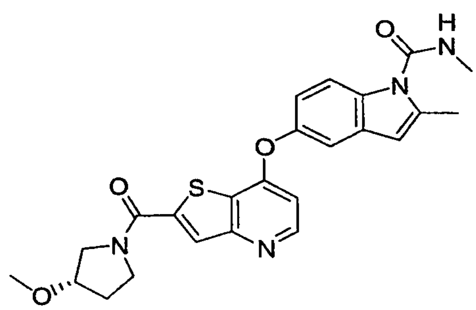
Example 4(e) was prepared in a similar manner as Example 4(a) except that 2R-methoxymethyl-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in step (i). ^{1}H NMR (300 MHz, CD_3OD) δ 8.45 (1H, d, J = 5.5 Hz), 7.87 (1H, s), 7.70 (1H, d, J = 8.97 Hz), 7.31 (1H, d, J = 2.38 Hz), 7.02 (1H, dd, J = 8.79, 2.38 Hz), 6.65 (1H, d, J = 5.67 Hz), 6.36 (1H, s), 4.42 (1H, m), 3.88 (2H, m), 3.61 (2H, m), 3.37 (3H, s), 3.01 (3H, s), 2.54 (3H, bs), 1.90-2.15 (4H, m). MS (ESI+) [M+H]/z Calc'd 479, found 479. Anal. ($C_{25}H_{26}N_4O_4S$) C, H, N.

Example 4(f): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



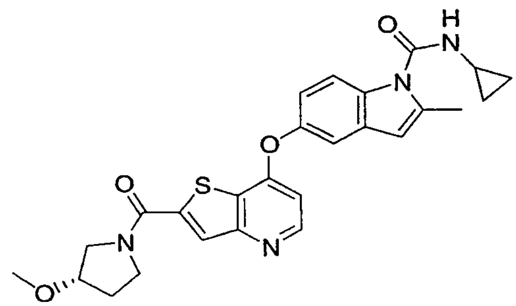
Example 4(f) was prepared in a similar manner as Example 4(c) except that 3S-methoxy-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in referenced step for Example 4(a), step (i). ^{1}H NMR (300 MHz, CD_3OD) δ 8.46 (1H, d, J = 5.27 Hz), 7.91 (1H, d, J = 5.84 Hz), 7.76 (1H, d, J = 8.85 Hz), 7.33 (1H, d, J = 2.07 Hz), 7.04 (1H, dd, J = 8.85, 2.26 Hz), 6.66 (1H, d, J = 5.65 Hz), 6.36 (1H, s), 4.21 (2H, d, J = 2.45 Hz), 4.12 (1H, m), 3.96 (2H, m), 3.75 (2H, m), 3.38 (s, 1.5H), 3.33 (s, 1.5H), 2.72 (1H, t, J = 2.45 Hz), 2.55 (3H, s), 2.15 (2H, m). MS (ESI+) [M+H]/z Calc'd 489, found 489. Anal. ($C_{26}H_{24}N_4O_4S$) C, H, N.

Example 4(g): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



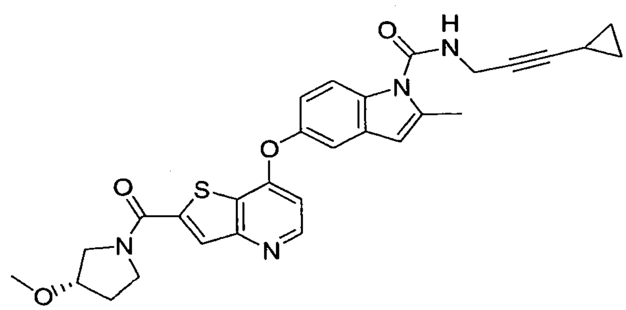
Example 4(g) was prepared in a similar manner as Example 4(a) except that 3S-methoxy-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in step (i). ^{1}H NMR (300 MHz, CD_3OD) δ 8.46 (1H, d, J = 5.46 Hz), 7.89 (1H, d, J = 5.65 Hz), 7.69 (1H, d, J = 8.85 Hz), 7.30 (1H, d, J = 2.07 Hz), 7.02 (1H, dd, J = 8.85, 2.07 Hz), 6.65 (1H, d, J = 5.46 Hz), 6.37 (1H, s), 4.11 (1H, m), 3.96 (2H, m), 3.74 (2H, m), 3.38 (s, 1.5H), 3.33 (s, 1.5H), 3.01 (3H, s), 2.54 (3H, s), 2.16 (2H, m). MS (ESI+) [M+H]/z Calc'd 465, found 465. Anal. ($C_{24}H_{24}N_4O_4S$) C, H, N.

Example 4(h): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



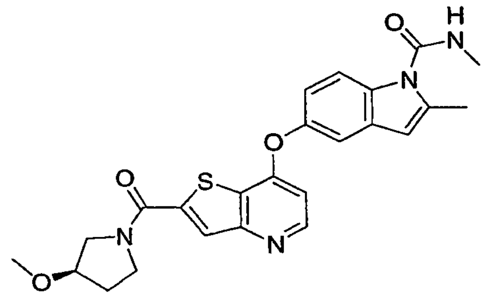
Example 4(h) was prepared in a similar manner as Example 4(g) except that cyclopropylamine was used instead of methylamine in the referenced step for Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.47 (1H, d, J = 4.90 Hz), 7.91 (1H, d, J = 6.03 Hz), 7.66 (1H, d, J = 8.85 Hz), 7.32 (1H, d, J = 2.07 Hz), 7.03 (1H, dd, J = 8.85, 2.45 Hz), 6.66 (1H, d, J = 5.27 Hz), 6.37 (1H, s), 4.12 (1H, m), 3.95 (2H, m), 3.70 (2H, m), 3.38 (s, 1.5H), 3.33 (s, 1.5H), 2.89 (1H, m), 2.52 (3H, s), 2.15 (2H, m), 0.87 (2H, m), 0.72 (2H, m). MS (ESI+) [M+H]/z Calc'd 491, found 491. Anal. ($C_{26}H_{26}N_4O_4S$) C, H, N.

Example 4(i): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (3-cyclopropyl-prop-2-ynyl)-amide



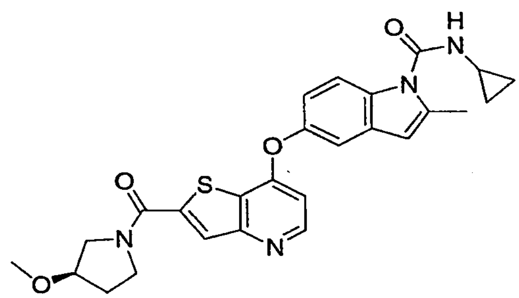
Example 4(i) was prepared in a similar manner as Example 4(g) except that 3-cyclopropyl-prop-2-ynylamine was used instead of methylamine in the referenced step for Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.47 (1H, d, J = 4.71 Hz), 7.91 (1H, d, J = 5.27 Hz), 7.73 (1H, d, J = 8.85 Hz), 7.31 (1H, d, J = 1.88 Hz), 7.03 (1H, dd, J = 8.85, 2.26 Hz), 6.66 (1H, d, J = 4.71 Hz), 6.37 (1H, s), 4.15 (2H, d, J = 1.70 Hz), 4.10 (1H, m), 3.95 (2H, m), 3.70 (2H, m), 3.38 (s, 1.5H), 3.33 (s, 1.5H), 2.54 (3H, s), 2.15 (2H, m), 1.28 (1H, m), 0.76 (2H, m), 0.64 (2H, m). MS (ESI+) [M+H]/z Calc'd 529, found 529. Anal. ($C_{29}H_{28}N_4O_4S$•$0.85CH_2Cl_2$) C, H, N.

Example 4(j): 5-[2-(3R-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



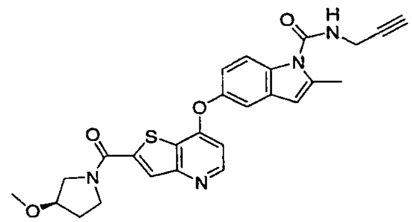
Example 4(j) was prepared in a similar manner as Example 4(a) except that 3R-methoxy-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in step (i). ^{1}H NMR (300 MHz, CD_3OD) δ 8.51 (1H, d, J = 5.5 Hz), 7.96 (1H, d, J = 5.06 Hz), 7.77 (1H, d, J = 8.8 Hz), 7.38 (1H, s), 7.08 (1H, dd, J = 8.8, 2.4 Hz), 6.72 (1H, d, J = 5.5 Hz), 6.41 (1H, s), 4.21-4.11 (1H, m), 4.11-3.95 (2H, m), 3.88-3.68 (2H, m), 3.39 (3H, d, J = 14.5 Hz), 3.07 (3H, s), 2.59 (3H, s), 2.38-2.07 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 465, found 465. Anal. ($C_{24}H_{24}N_4O_4S$•$0.2H_2O$) C, H, N.

Example 4(k): 5-[2-(3R-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



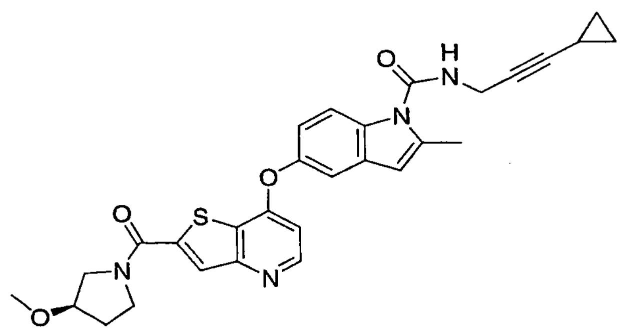
Example 4(k) was prepared in a similar manner as Example 4(j) except that cyclopropylamine was used instead of methylamine in the referenced step for Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.50 (1H, d, J = 5.5 Hz), 7.92 (1H, d, J = 5.5 Hz), 7.68 (1H, d, J = 8.8 Hz), 7.37 (1H, s), 7.08 (1H, dd, J = 8.8, 2.4 Hz), 6.68 (1H, d, J = 5.5 Hz), 6.40 (1H, s), 4.21-4.11 (1H, m), 4.08-3.90 (2H, m), 3.87-3.64 (2H, m), 3.39 (3H, d, J = 14.5 Hz), 2.97-2.86 (1H, m), 2.49 (3H, s), 2.38-2.07 (2H, m), 0.97-0.87 (2H, m), 0.78-0.69 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 491, found 491. Anal. ($C_{26}H_{26}N_4O_4S$•0.6EtOAc) C, H, N.

Example 4(l): 5-[2-(3R-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



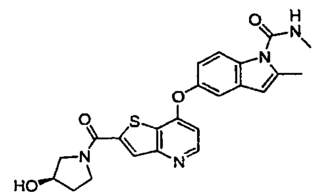
Example 4(l) was prepared in a similar manner as Example 4(j) except that propargylamine was used instead of methylamine in the referenced step for Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (1H, d, J = 5.5 Hz), 7.97 (1H, d, J = 5.1 Hz), 7.80 (1H, d, J = 8.5 Hz), 7.38 (1H, s), 7.08 (1H, dd, J = 8.8, 2.4 Hz), 6.72 (1H, d, J = 5.5 Hz), 6.43 (1H, s), 4.28 (2H, d, J = 1.9 Hz), 4.11-3.91 (3H, m), 3.88-3.68 (2H, m), 3.39 (3H, d, J = 14.5 Hz), 2.78-2.72 (1H, m), 2.59 (3H, s), 2.38-2.08 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 489, found 489. Anal. ($C_{26}H_{24}N_4O_4S$•0.5EtOAc) C, H, N.

Example 4(m): 5-[2-(3R-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (3-cyclopropyl-prop-2-ynyl)-amide



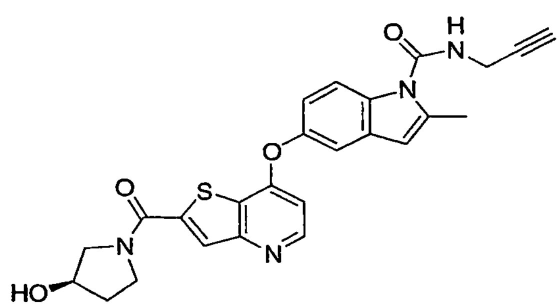
Example 4(m) was prepared in a similar manner as Example 4(j) except that 3-cyclopropyl-2-propynylamine was used instead of methylamine in the referenced step for Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.36 (1H, d, J = 5.5 Hz), 7.81 (1H, d, J = 5.0 Hz), 7.64 (1H, d, J = 8.8 Hz), 7.24 (1H, s), 6.95 (1H, dd, J = 8.8, 2.4 Hz), 6.68 (1H, d, J = 5.5 Hz), 6.29 (1H, s), 4.05 (2H, d, J = 1.9 Hz), 4.01-3.81 (3H, m), 3.73-3.57 (2H, m), 3.26 (3H, d, J = 14.5 Hz), 2.45 (3H, s), 2.19-1.88 (2H, m), 1.27-1.10 (1H, m), 0.71-0.62 (2H, m), 0.56-0.51 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 529, found 529. Anal. ($C_{29}H_{28}N_4O_4S$•0.6H_2O) C, H, N.

Example 4(n): 5-[2-(3R-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



A solution of 5-[2-(3R-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide (50 mg, 0.087 mmol), prepared in Example 4(j), in CH_2Cl_2 (3 mL) was cooled to 0°C, 0.1 mL of 1.0 M BBr_3 in CH_2Cl_2 was added. The mixture was stirred at 0°C for 15 minutes, and was then warmed to room temperature. After being stirred at room temperature for 2 hours, methanol (0.5 mL) was added, and the mixture was basified with concentrated NH_4OH to pH ~8. The resulting solution was stirred at room temperature for 1 hour, and extracted with CH_2Cl_2. The combined organic layer was dried with Na_2SO_4, concentrated to give the crude product. Elution with EtOAc : CH_2Cl_2 : MeOH (1:1:0.1) through a flash column and subsequent concentration provided the product as a white solid (24 mg, 78% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.55 (1H, d, J = 5.5 Hz), 7.92 (1H, d, J = 17.7 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.37 (1H, s), 7.08 (1H, dd, J = 8.8, 2.4 Hz), 6.71 (1H, d, J = 5.5 Hz), 6.40 (1H, s), 4.57 (1H, bs), 4.15-3.98 (2H, m), 3.87-3.78 (2H, m), 3.77-3.51 (1H, m), 3.05 (3H, s), 2.48 (3H, s), 2.22-2.00 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 451, found 451. Anal. ($C_{23}H_{22}N_4O_4S$•0.7EtOAc•1.0H_2O) C, H, N.

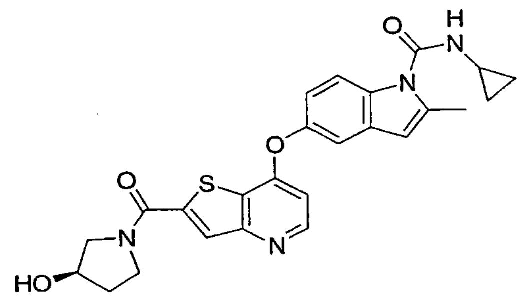
Example 4(o): 5-[2-(3R-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 4(o) was prepared in a similar manner as Example 4(n) except that the starting material was Example 4(l). ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (1H, d, J = 5.5 Hz),

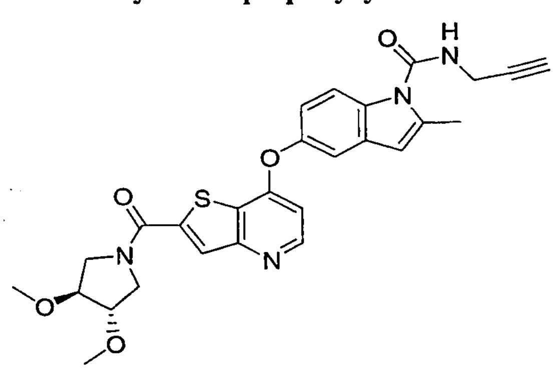
7.95 (1H, d, J = 17.7 Hz), 7.80 (1H, d, J = 8.8 Hz), 7.38 (1H, s), 7.10 (1H, dd, J = 8.8, 2.4 Hz), 6.72 (1H, d, J = 5.5 Hz), 6.42 (1H, s), 4.57 (1H, bs), 4.27 (2H, d, J = 1.9 Hz), 4.17-4.02 (2H, m), 3.87-3.78 (2H, m), 3.77-3.51 (1H, m), 2.78-2.72 (1H, m), 2.49 (3H, s), 2.23-2.01 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 475, found 475. Anal. ($C_{25}H_{22}N_4O_4S$•$0.4CH_2Cl_2$) C, H, N.

Example 4(p): 5-[2-(3R-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



Example 4(p) was prepared in a similar manner as Example 4(n) except that Example 4(k) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.29 (1H, d, J = 5.6 Hz), 7.73 (1H, d, J = 17.7 Hz), 7.48 (1H, d, J = 8.8 Hz), 7.11 (1H, s), 6.82 (1H, dd, J = 8.7, 2.1 Hz), 6.46 (1H, d, J = 5.5 Hz), 6.19 (1H, s), 4.29 (1H, bs), 3.91-3.74 (2H, m), 3.61-3.53 (2H, m), 3.53-3.48 (1H, m), 2.71-2.55 (1H, m), 2.36 (3H, s), 1.93-1.73 (2H, m), 0.68-0.60 (2H, m), 0.55-0.50 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 477, found 477. Anal. ($C_{25}H_{24}N_4O_4S$•1.0MeOH•1.5EtOAc) C, H, N.

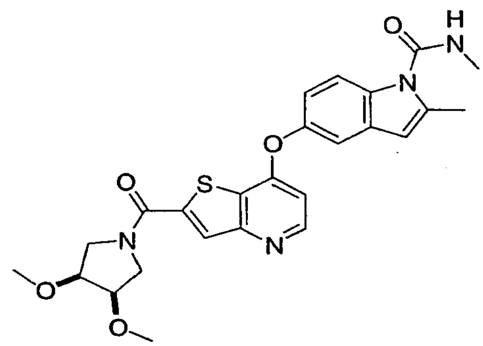
Example 4(q): 5-[2-(3S,4S-Dimethoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 4(q) was prepared in a similar manner as Example 4(l) except that 3S,4S-dimethoxy-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in step (i) of

Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.37 (1H, d, *J* = 5.46 Hz), 7.81 (1H, s), 7.66 (1H, d, *J* = 8.85 Hz), 7.23 (1H, s), 6.95 (1H, d, *J* = 8.85 Hz), 6.56 (1H, d, *J* = 5.47 Hz), 6.29 (1H, s), 4.11 (2H, s), 3.81-3.96 (4H, m), 3.66 (2H, m), 3.34 (3H, s), 3.29 (3H, s), 2.63 (1H, m), 2.46 (3H, m). MS (ESI+) [M+H]/z Calc'd 519, found 519. Anal. ($C_{27}H_{26}N_4O_5S$•$0.5H_2O$) C, H, N.

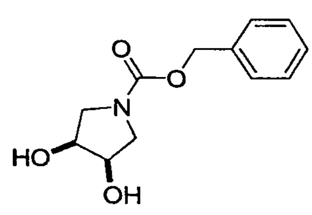
Example 4(r): 5-[2-(3,4-*cis*-Dimethoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



Example 4(r) was prepared in a similar manner as Example 4(a) except that 3,4-*cis*-Dimethoxy-pyrrolidine, prepared as described below, was used instead of 2S-methoxymethyl-pyrrolidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, 1H, *J* = 5.46 Hz), 7.85 (s, 1H), 7.72 (d, 1H, *J* = 8.85 Hz), 7.28 (d, 1H, *J* = 2.26 Hz), 7.03 (dd, 1H, *J* = 8.85, 2.26 Hz), 6.58 (d, 1H, *J* = 5.27 Hz), 6.30 (s, 1H), 5.77 (d, 1H, *J* = 4.52 Hz), 3.72-4.10 (m, 6H), 3.50 (s, 3H), 3.47 (s, 3H), 3.13 (s, 1.5H), 3.12 (s, 1.5H), 2.61 (s, 3H). MS (ESI+) [M+H]/z Calc'd 495, found 495. Anal. ($C_{25}H_{26}N_4O_5S$•0.15Hexane) C, H, N.

The starting materials were prepared as follows:

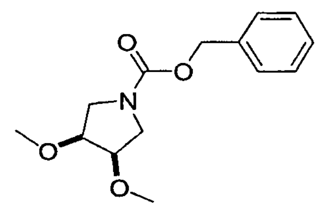
(i) 3,4-*cis*-Dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester



To a solution of benzyl 3-pyrroline-1-carboxylate (15 g, 90%, 66.4 mmol) in 100 mL THF and 25 mL water was added osmium tetroxide (10 mL, 2.5 wt. % solution in 2-methyl-2-propanol, 0.8 mmol) and 4-methylmorpholine N-oxide (8.56 g, 73 mmol) as solid. The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue

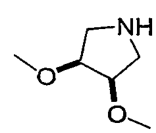
was re-dissolved in 300 mL ethyl acetate and washed with aqueous Na_2SO_3 (1.5 g in 100 mL water) solution and aqueous $NaHCO_3$ solution and brine. The combined aqueous layer was extracted once with ethyl acetate (100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was further purified by flash column chromatography eluting with 4-5 % MeOH in CH_2Cl_2 to give 15.26 g product as white solid (97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.11 (bs, 2H), 4.26 (m, 2H), 3.66 (m, 2H), 3.41 (m, 2H), 1.56 (bs, 2H).

(ii) 3,4-*cis*-Dimethoxy-pyrrolidine-1-carboxylic acid benzyl ester



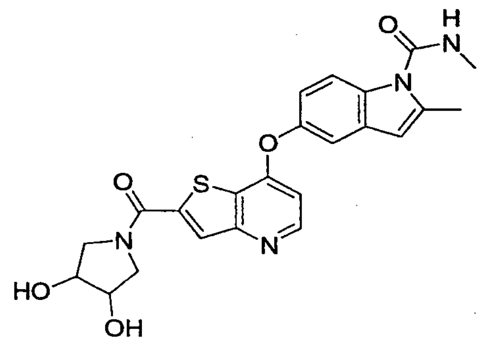
To a stirred solution of 3,4-*cis*-dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester (15.2 g, 64.3 mmol) in 130 mL anhydrous THF was added iodomethane (36 g, 257 mmol) at 0°C; sodium hydride (6.4 g, 60% in mineral oil, 160 mmol) was then added slowly as solid at 0°C. The mixture was allowed to warm to room temperature and stirred at room temperature for 3 hours. 30 mL 1N aqueous HCl was then added to the mixture which was concentrated *in vacuo* to remove THF. The residue was re-dissolved in 300 mL ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was further purified by flash column chromatography eluting with 5-25 % EtOAc in CH_2Cl_2 to give 17 g product as yellow oil (99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.12 (m, 2H), 3.87 (m, 2H), 3.55 (m, 2H), 3.42 (bs, 6H), 1.58 (s, 2H).

(iii) 3,4-*cis*-Dimethoxy-pyrrolidine



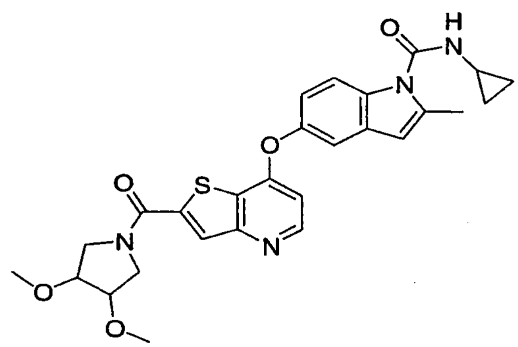
To a stirred solution of 3,4-*cis*-dimethoxy-pyrrolidine-1-carboxylic acid benzyl ester (16.95 g, 63.88 mmol) in 150 mL MeOH was added 1.3 g Pd on C (10% w/w). The mixture was stirred under H_2 balloon at room temperature for 3 hours and filtered through celite. The filtrate was concentrated *in vacuo*, re-dissolved in CH_2Cl_2 and dried over Na_2SO_4. The solution was concentrated to give 8.3 g product as yellow oil (99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (m, 2H), 3.47 (bs, 2H), 3.41 (s, 6H), 3.01 (bs, 2H).

Example 4(s): 5-[2-(3,4-*cis*-Dihydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



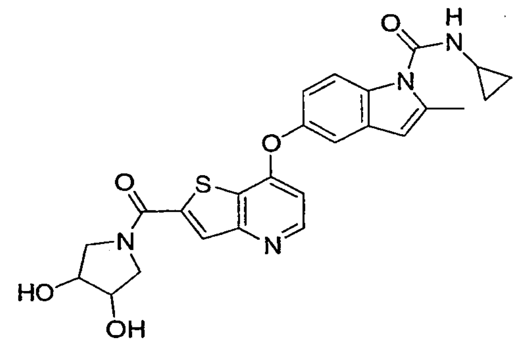
Example 4(s) was prepared in a similar manner as Example 4(n) except that Example 4(r) was used as starting material. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.54 (d, 1H, J = 4.90 Hz), 7.96 (s, 1H), 7.64 (d, 1H, J = 8.48 Hz), 7.38 (s, 1H), 7.01 (d, 1H, J = 8.85 Hz), 6.59 (d, 1H, J = 5.27 Hz), 6.35 (s, 1H), 3.95-4.20 (m, 4H), 3.58-3.70 (m, 2H), 2.87 (s, 3H), 2.50 (s, 3H). MS (ESI+) [M+H]/z Calc'd 467, found 467. Anal. ($C_{23}H_{22}N_4O_5S{\bullet}0.07CH_2Cl_2$) C, H, N.

Example 4(t): 5-[2-(3,4-*cis*-Dimethoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



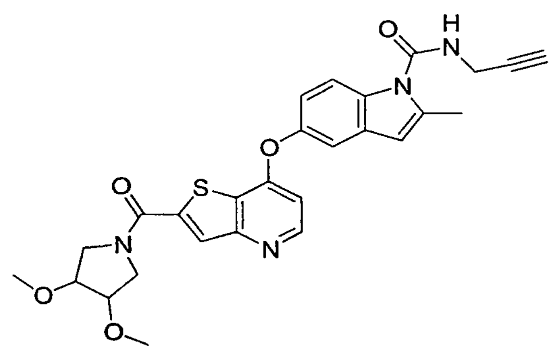
Example 4(t) was prepared in a similar manner as Example 4(r) except that cyclopropylamine was used instead of methylamine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H, J = 5.46 Hz), 7.82 (s, 1H), 7.62 (d, 1H, J = 8.85 Hz), 7.25 (bs, 1H), 6.98 (dd, 1H, J = 8.85, 2.26 Hz), 6.55 (d, 1H, J = 5.46 Hz), 6.29 (s, 1H), 6.05 (s, 1H), 3.65-4.08 (m, 6H), 3.48 (s, 3H), 3.45 (s, 3H), 2.91 (m, 1H), 2.57 (s, 3H), 0.93 (m, 2H), 0.75 (m, 2H). MS (ESI+) [M+H]/z Calc'd 521, found 521. Anal. ($C_{27}H_{28}N_4O_5S{\bullet}0.2$Hexane) C, H, N.

Example 4(u): 5-[2-(3,4-*cis*-Dihydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



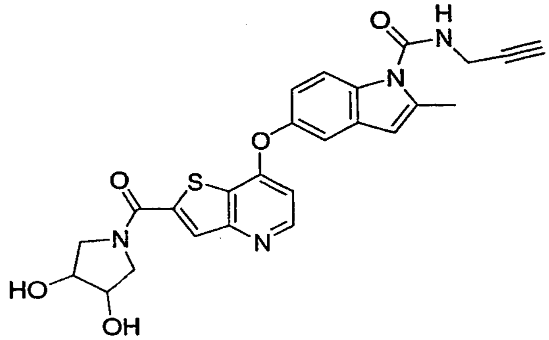
Example 4(u) was prepared in a similar manner as Example 4(n) except that Example 4(t) was used as starting material. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.54 (d, 1H, J = 5.46 Hz), 7.97 (s, 1H), 7.59 (d, 1H, J = 8.85 Hz), 7.39 (d, 1H, J = 2.26 Hz), 7.06 (dd, 1H, J = 8.85, 2.26 Hz), 6.64 (d, 1H, J = 5.27 Hz), 6.39 (s, 1H), 3.95-4.18 (m, 4H), 3.65 (m, 2H), 3.86 (m, 1H), 2.47 (s, 3H), 0.75 (m, 2H), 0.66 (m, 2H). MS (ESI+) [M+H]/z Calc'd 493, found 493. Anal. ($C_{25}H_{24}N_4O_5S$•$0.2CH_2Cl_2$) C, H, N.

Example 4(v): 5-[2-(3,4-*cis*-Dimethoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



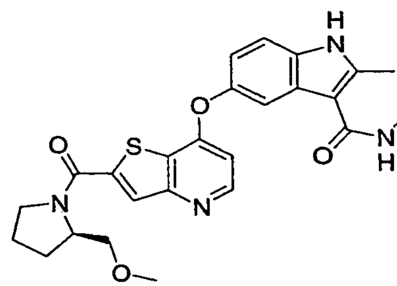
Example 4(v) was prepared in a similar manner as Example 4(r) except that propargylamine was used instead of methylamine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 1H, J = 5.46 Hz), 7.82 (s, 1H), 7.76 (d, 1H, J = 8.85 Hz), 7.26 (bs, 1H), 7.01 (dd, 1H, J = 8.85, 2.26 Hz), 6.55 (d, 1H, J = 5.46 Hz), 6.31 (s, 1H), 6.21 (bs, 1H), 4.30 (m, 2H), 3.70-4.10 (m, 6H), 3.48 (s, 3H), 3.45 (s, 3H), 2.59 (s, 3H), 2.35 (t, 1H, J = 2.45 Hz). MS (ESI+) [M+H]/z Calc'd 519, found 519. Anal. ($C_{27}H_{26}N_4O_5S$•0.15Hexane) C, H, N.

Example 4(w): 5-[2-(3,4-*cis*-Dihydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



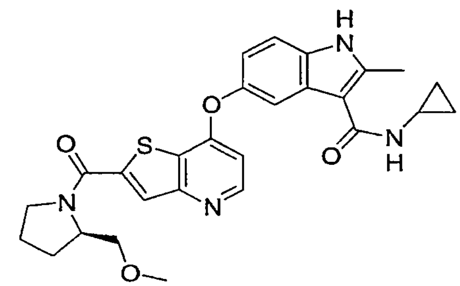
Example 4(w) was prepared in a similar manner as Example 4(n) except that Example 4(v) was used as starting material. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.54 (d, 1H, J = 5.27 Hz), 7.97 (s, 1H), 7.70 (d, 1H, J = 8.85 Hz), 7.42 (d, 1H, J = 1.88 Hz), 7.09 (dd, 1H, J = 8.67, 1.88 Hz), 6.67 (d, 1H, J = 5.27 Hz), 6.40 (s, 1H), 4.11 (m, 4H), 4.00 (m, 2H), 3.65 (m, 2H), 2.50 (bs, 4H). MS (ESI+) [M+H]/z Calc'd 491, found 491. Anal. ($C_{25}H_{22}N_4O_5S{\bullet}0.7H_2O$) C, H, N.

Example 4(x): 5-[2-(2R-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-yloxy]-2-methyl-1*H*-indole-3-carboxylic acid methylamide



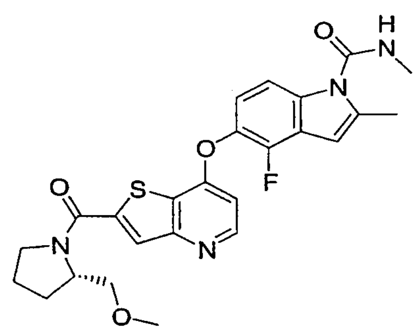
A solution of 40 mg 5-[2-(2R-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide , Example 4(e), in 20 mL 1:1 CH_3CN and H_2O with 1% TFA was kept at room temperature overnight. The mixture was concentrated *in vacuo*, re-dissolved in EtOAc, and washed with aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography eluting with 4-8% MeOH in CH_2Cl_2 to give 25 mg desired product (63% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.45 (d, 1H, J = 5.5 Hz), 7.87 (s, 1H), 7.65 (d, 1H, J = 2.2 Hz), 7.51 (bs, 1H), 7.43 (d, 1H, J = 8.8 Hz), 7.00 (dd, 1H, J = 8.6, 2.2 Hz), 6.67 (d, 1H, J = 5.5 Hz), 4.43 (m, 1H), 3.89 (m, 2H), 3.62 (m, 2H), 3.37 (s, 3H), 2.90 (s, 3H), 2.65 (s, 3H), 1.94-2.18 (m, 4H). MS (ESI+) [M+H]/z Calc'd 479, found 479.

Example 4(y): 5-[2-(2R-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*] pyridin-7-yloxy]-2-methyl-1*H*-indole-3-carboxylic acid cyclopropylamide



Example 4(y) was prepared in a similar manner as Example 4(x) except that cyclopropylamine was used instead of methylamine. . ^{1}H NMR (300 MHz, CD_3OD) δ 8.43 (d, 1H, J = 5.5 Hz), 7.85 (s, 1H), 7.78 (bs, 1H), 7.58 (d, 1H, J = 2.2 Hz), 7.40 (d, 1H, J = 8.6 Hz), 6.98 (dd, 1H, J = 8.6, 2.4 Hz), 6.65 (d, 1H, J = 5.5 Hz), 4.42 (m, 1H), 3.88 (m, 2H), 3.60 (m, 2H), 3.36 (s, 3H), 2.79 (m, 1H), 2.62 (s, 3H), 1.90-2.18 (m, 4H), 0.76 (m, 2H), 0.61 (m, 2H). MS (ESI+) [M+H]/z Calc'd 505, found 505.

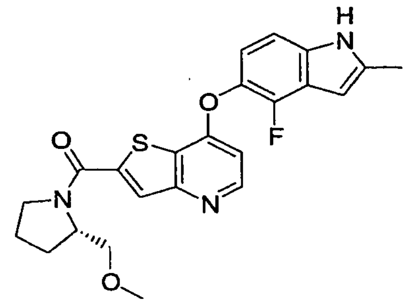
Example 5(a): 4-Fluoro-5-[2-(2S-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



Example 5(a) was prepared in a similar manner as Example 4(a) except that 4-fluoro-2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1-(4-nitrophenoxy)indole, prepared as described below was used instead of 2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1-(4-nitrophenoxy)indole. ^{1}H NMR (300 MHz, CD_3OD) δ 8.40 (1H, d, J = 5.24 Hz), 7.81 (1H, s), 7.42 (1H, d, J = 8.85 Hz), 7.04 (1H, m), 6.56 (1H, d, J = 5.28 Hz), 6.38 (1H, s), 4.33 (1H, m), 3.80 (2H, m), 3.52 (2H, m), 3.27 (3H, s), 2.91 (3H, s), 2.45 (3H, s), 1.87-2.09 (4H, m). MS (ESI+) [M+H]/z Calc'd 497, found 497. Anal. ($C_{25}H_{25}FN_4O_4S$•1.0MeOH) C, H, N.

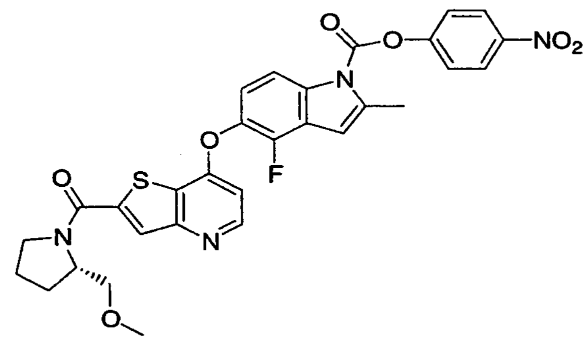
The starting materials were prepared as follows:

(i) [7-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-thieno[3,2-*b*]pyridin-2-yl]-(2S-methoxymethyl-pyrrolidin-1-yl)-methanone



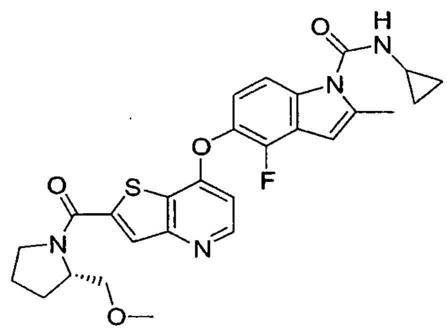
The title compound was prepared in a similar manner as Example 4(a), step (ii) except that 4-fluoro-5-hydroxy-2-methylindole was used instead of 5-hydroxy-2-methylindole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (1H, d, *J* = 5.47 Hz), 8.42 (1H, bs), 7.84 (1H, bs), 7.08 (1H, d, *J* = 8.67 Hz), 6.92-6.97 (1H, m), 6.54 (1H, d, *J* = 5.46 Hz), 6.34 (1H, bs), 4.49-4.52 (1H, m), 3.81-3.86 (2H, m), 3.57-3.65 (2H, m), 3.37 (3H, s), 2.46 (3H, s), 1.89-2.10 (4H, m). MS (ESI+) [M+H]/z Calc'd 440, found 440.

(ii) 4-fluoro-2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1-(4-nitrophenoxy)indole



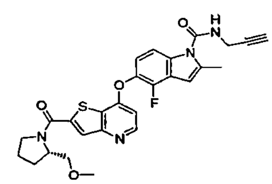
The title compound was prepared as described for Example 4(a), step (iii): ^{1}H NMR ($CHCl_3$) □8.52 (d, 1H, *J* = 5.47 Hz), 8.39 (d, 2H, J = 9.23 Hz), 7.85 (s, 1H), 7.42 (d, 1H, *J* = 8.85 Hz), 7.52 (d, 2H, *J* = 9.23 Hz), 7.15-7.21 (m, 1H), 6.92 (d, 1H, *J* = 9.24 Hz), 6.61 (s, 1H), 4.28-4.51 (m, 1H), 3.85 (m, 2H), 3.64 (m, 2H), 3.37 (s, 3H), 2.72 (s, 3H), 1.97-2.08 (m, 2H), 1.55-1.64 (m, 2H). Rf = 0.65 (10% CH_3OH in 1:1 CH_2Cl_2/EtOAc).

Example 5(b): 4-Fluoro-5-[2-(2S-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



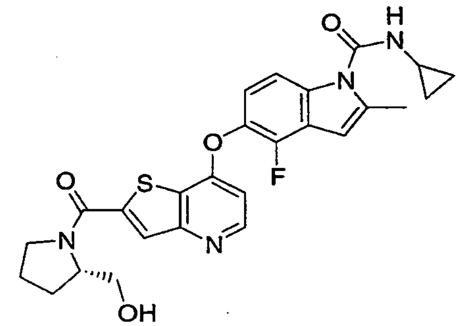
Example 5(b) was prepared in a similar manner as Example 5(a) except that cyclopropylamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.40 (1H, d, *J* = 5.47 Hz), 7.82 (1H, bs), 7.37 (1H, d, *J* = 8.85 Hz), 7.01-7.07 (1H, m), 6.56 (1H, d, *J* = 5.46 Hz), 6.38 (1H, s), 4.34 (1H, bs), 3.80 (2H, m), 3.53 (2H, m), 3.33 (3H, m), 2.77-2.84 (1H, m), 2.44 (3H, s), 1.78-2.05 (4H, m), 0.75-0.79 (2H, m), 0.60-0.65 (2H, m). MS (ESI+) [M+H]/z Calc'd 523, found 523. Anal. ($C_{27}H_{27}FN_4O_4S \bullet 0.25H_2O$) C, H, N.

Example 5(c): 4-Fluoro-5-[2-(2S-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



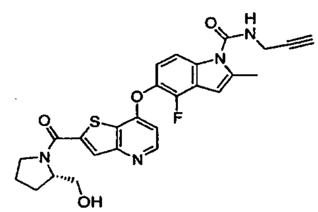
Example 5(c) was prepared in a similar manner as Example 5(a) except that propargylamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.53 (1H, d, *J* = 5.65 Hz), 7.95 (1H, s), 7.60 (1H, d, *J* = 8.85 Hz), 7.16-7.22 (1H, m), 6.71 (1H, d, *J* = 5.46 Hz), 6.53 (1H, s), 4.43 (1H, bs), 4.12 (2H, m), 3.80 (2H, m), 3.53 (2H, m), 3.33 (3H, s), 2.63-2.65 (1H, m), 2.47 (3H, s), 1.85-2.04 (4H, m). MS (ESI+) [M+H]/z Calc'd 521, found 521. Anal. ($C_{27}H_{25}FN_4O_4S$) C, H, N.

Example 5(d): 4-Fluoro-5-[2-(2S-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



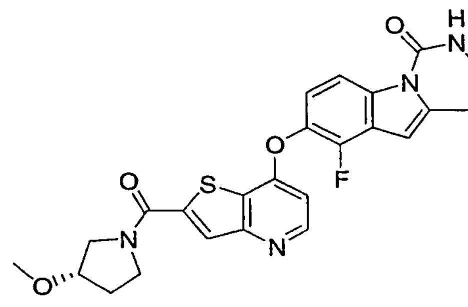
Example 5(d) was prepared in a similar manner as Example 4(n) except that Example 5(b) was used as starting material. [1]H NMR (300 MHz, CD_3OD) δ 8.40 (1H, d, J = 5.46 Hz), 7.83 (1H, s), 7.35 (1H, d, J = 8.86 Hz), 7.01-7.07 (1H, m), 6.56 (1H, d, J = 5.46 Hz), 6.38 (1H, s), 4.25 (1H, bs), 3.66-3.81 (2H, m), 3.19-3.21 (2H, m), 2.76-2.82 (1H, m), 2.43 (3H, s), 1.98-2.02 (4H, m), 0.75-0.79 (2H, m), 0.60-0.65 (2H, m). MS (ESI+) [M+H]/z Calc'd 509, found 509. Anal. ($C_{26}H_{25}FN_4O_4S$•$0.75CH_2Cl_2$) C, H, N.

Example 5(e): 4-Fluoro-5-[2-(2S-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



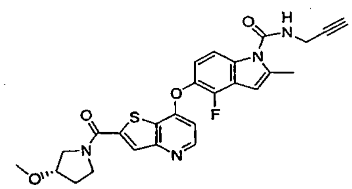
Example 5(e) was prepared in a similar manner as Example 4(n) except that Example 5(c) was used as starting material. [1]H NMR (300 MHz, CD_3OD) δ 8.41 (1H, d, J = 5.46 Hz), 7.83 (1H, s), 7.48 (1H, d, J = 8.85 Hz), 7.04-7.07 (1H, m), 6.58 (1H, d, J = 5.46 Hz), 6.40 (1H, s), 4.26-4.28 (1H, m), 4.12-4.13 (2H, m), 3.66-3.83 (2H, m), 3.19-3.22 (2H, m), 2.63-2.65 (1H, m), 2.47 (3H, s), 1.99-2.02 (4H, m). MS (ESI+) [M+H]/z Calc'd 507, found 507. Anal. ($C_{26}H_{23}FN_4O_4S$•$0.5MeOH$) C, H, N.

Example 5(f): 4-Fluoro-5-[2-(3S-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



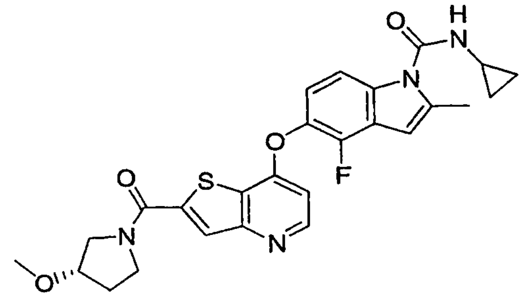
Example 5(f) was prepared in a similar manner as Example 5(a) except that 3S-methoxy-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in the referenced step (i) of Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (1H, d, *J* = 5.1 Hz), 7.84 (1H, d, *J* = 6.2 Hz), 7.43 (1H, d, *J* = 8.8 Hz), 7.05 (1H, dd, *J* = 8.8, 1.3 Hz), 6.58 (1H, d, *J* = 5.5 Hz), 6.39 (1H, s), 4.07-3.80 (3H, m), 3.74-3.58 (2H, m), 3.27 (3H, d, *J* = 14.3 Hz), 2.97 (3H, s), 2.46 (3H, s), 2.08-1.94 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 483, found 483. Anal. ($C_{24}H_{23}N_4O_4SF$•0.5EtOAc) C, H, N.

Example 5(g): 4-Fluoro-5-[2-(3S-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



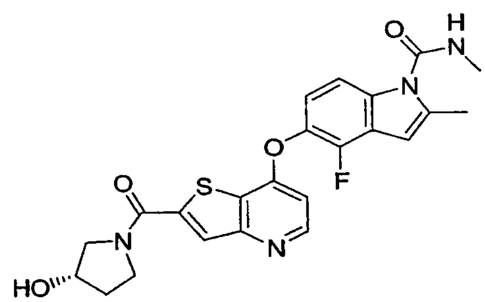
Example (g) was prepared in a similar manner as Example 5(f) except that propargylamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.40 (1H, d, *J* = 5.5 Hz), 7.83 (1H, d, *J* = 5.8 Hz), 7.47 (1H, d, *J* = 8.8 Hz), 7.06 (1H, dd, *J* = 8.7, 1.0 Hz), 6.58 (1H, d, *J* = 5.5 Hz), 6.40 (1H, s), 4.12 (2H, d, *J* = 2.4 Hz), 4.08-3.78 (3H, m), 3.75-3.55 (2H, m), 3.42 (3H, d, *J* = 14.3 Hz), 2.66-2.60 (1H, m), 2.47 (3H, s), 2.21-1.94 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 507, found 507. Anal. ($C_{26}H_{23}N_4O_4SF$) C, H, N.

Example 5(h): 4-Fluoro-5-[2-(3S-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



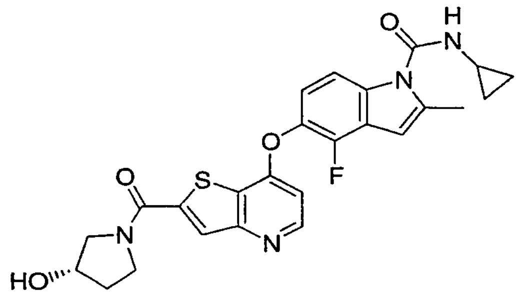
Example 5(h) was prepared in a similar manner as Example 5(f) except that cyclopropylamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (1H, d, J = 5.5 Hz), 7.94 (1H, d, J = 6.2 Hz), 7.48 (1H, d, J = 8.8 Hz), 7.15 (1H, dd, J = 8.7, 0.8 Hz), 6.68 (1H, d, J = 5.3 Hz), 6.49 (1H, s), 4.20-4.89 (3H, m), 3.85-3.69 (2H, m), 3.40 (3H, d, J = 14.3 Hz), 2.93-2.84 (1H, m), 2.56(3H, s), 2.33-2.06 (2H, m), 0.94-0.84 (2H, m), 0.78-0.70 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 509, found 509. Anal. ($C_{26}H_{25}N_4O_4SF$) C, H, N.

Example 5(i): 4-Fluoro-5-[2-(3S-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



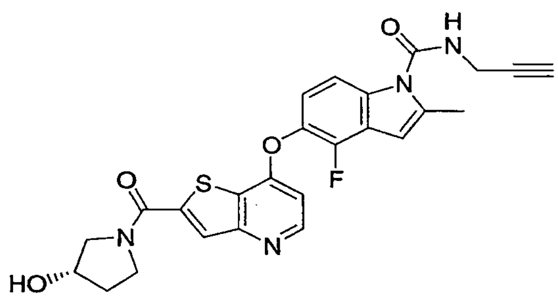
Example 5(i) was prepared in a similar manner as Example 4(n) except that 5(f) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.54 (1H, d, J = 5.5 Hz), 7.97 (1H, d, J = 17.5 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.18 (1H, dd, J = 8.7, 1.1 Hz), 6.70 (1H, d, J = 5.5 Hz), 6.52 (1H, s), 4.53 (1H, bs), 4.12-4.01 (2H, m), 3.87-3.77 (2H, m), 3.77-3.70 (1H, m), 3.04 (3H, s), 2.59 (3H, s), 2.24-1.99 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 469, found 469. Anal. ($C_{23}H_{21}N_4O_4SF \cdot 0.5CH_2Cl_2$) C, H, N.

Example 5(j): 4-Fluoro-5-[2-(3S-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropylamide



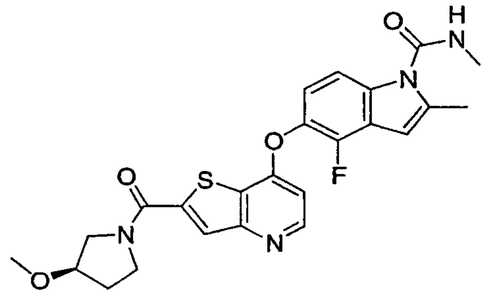
Example 5(j) was prepared in a similar manner as Example 4(n) except that 5(h) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.40 (1H, bs), 7.97 (1H, d, J = 17.5 Hz), 7.35 (1H, d, J = 8.8 Hz), 7.04 (1H, dd, J = 8.8, 1.3 Hz), 6.56 (1H, d, J = 5.5 Hz), 6.37 (1H, s), 4.41 (1H, bs), 4.00-3.89 (2H, m), 3.75-3.64 (2H, m), 3.62-3.56 (1H, m), 2.83-2.76 (1H, m), 2.43 (3H, s), 2.05-1.96 (2H, m), 0.83-0.74 (2H, m), 0.65-0.58 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 495, found 495. Anal. ($C_{25}H_{23}N_4O_4SF$•0.6EtOAc) C, H, N.

Example 5(k): 4-Fluoro-5-[2-(3R-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



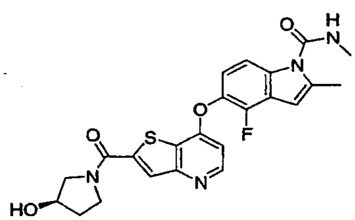
Example 5(k) was prepared in a similar manner as Example 4(n) except that Example 5(g) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.54 (d, 1H, J = 5.7 Hz), 7.97 (d, 1H, J = 17.5 Hz), 7.59 (d, 1H, J = 9.0 Hz), 7.12 (dd, 1H, J = 8.7, 0.9 Hz), 6.71 (d, 1H, J = 5.5 Hz), 6.53 (s, 1H), 4.55 (bs, 1H), 4.26 (d, 2H, J = 2.6 Hz), 4.16-4.01 (m, 2H), 3.88-3.77 (m, 2H), 3.77-3.70 (m, 1H), 2.78-2.73 (m, 1H), 2.60 (s, 3H), 2.22-2.12 (m, 2H). LCMS (ESI+) [M+H]/z Calc'd 493, found 493. Anal. ($C_{25}H_{21}N_4O_4SF$•MeOH) C, H, N.

Example 5(l): 4-Fluoro-5-[2-(3R-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



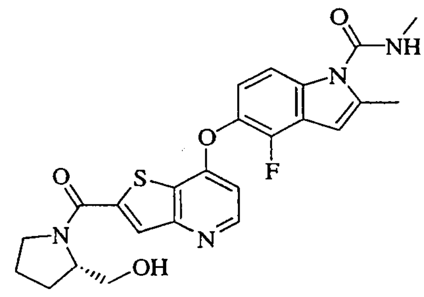
Example 5(l) was prepared in a similar manner as Example 5(a) except that 3R-methoxy-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in the referenced step (i) of Example 4(a). . ^{1}H NMR (300 MHz, CD_3OD) δ 8.36 (d, 1H, J = 5.5 Hz), 7.81 (d, 1H, J = 5.3 Hz), 7.41 (d, 1H, J = 8.8 Hz), 7.02 (dd, 1H, J = 8.7, 0.9 Hz), 6.55 (d, 1H, J = 8.3 Hz), 6.36 (s, 1H), 4.08-3.75 (m, 3H), 3.73-3.51 (m, 2H), 3.26 (d, 3H, J = 14.3 Hz), 2.91 (s, 3H), 2.44 (s, 3H), 2.21-1.93 (m, 2H). LCMS (ESI+) [M+H]/z Calc'd 483, found 483. Anal. ($C_{24}H_{23}N_4O_4SF$) C, H, N.

Example 5(m): 4-Fluoro-5-[2-(3R-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



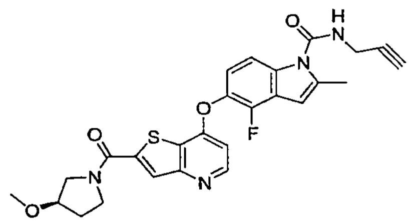
Example 5(m) was prepared in a similar manner as Example 4(n) except that Example 5(l) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (d, 1H, J = 5.5 Hz), 7.82 (d, 1H, J = 17.3 Hz), 7.41 (d, 1H, J = 8.9 Hz), 7.03 (dd, 1H, J = 8.7, 0.7 Hz), 6.56 (d, 1H, J = 5.5 Hz), 6.37 (s, 1H), 4.41 (bs, 1H), 4.01-3.88 (m, 2H), 3.75-3.63 (m, 2H), 3.63-3.54(m, 1H), 2.91 (s, 3H), 2.45 (s, 3H), 2.21-1.93 (m, 2H). LCMS (ESI+) [M+H]/z Calc'd 469, found 469. Anal. ($C_{23}H_{21}N_4O_4SF$•$0.4CH_2Cl_2$) C, H, N.

Example 5(n): 4-Fluoro-5-[(2-{[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl} thieno[3,2-*b*]pyridin-7-yl)oxy]-*N*,2-dimethyl-1*H*-indole-1-carboxamide



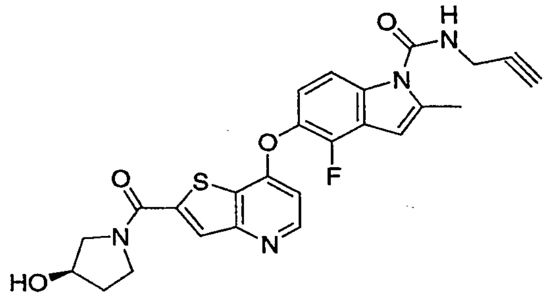
Example (5n) was prepared in a similar manner as Example (4n) except that Example 5(a) was used as starting material. ^{1}H NMR (CD_3OD) δ 8.40 (1H, d, J = 5.5 Hz), 7.83 (1H,s), 7.42 (1H, d, J = 8.9 Hz), 7.04 (1H, s), 6.57 (1H, d, J = 5.5 Hz), 6.39 (1H, s), 4.25 (1H, s), 3.81-3.60 (4H, m), 2.91 (3H, s), 2.46 (3H, s), 2.04-1.98 (2H, m), 0.81-0.75 (2H, m). HRMS Calc'd for $C_{24}H_{23}FN_4O_4S$ [MH^+] 483.1499; Found 483.1502.

Example 5(o): 4-Fluoro-5-[2-((R)-3-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



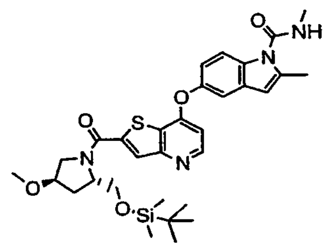
Example (5o) was prepared in a similar manner as Example (5l) except that propargylamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (1H, d, J = 5.7 Hz), 7.94 (1H, d, J = 5.3 Hz), 7.58 (1H, d, J = 8.9 Hz), 7.17 (1H, dd, J = 1.1, 8.9 Hz), 6.69 (1H, d, J = 5.7 Hz), 6.51 (1H, s), 4.26 (2H, d, J = 2.5 Hz), 4.17-3.93 (3H, m), 3.88-3.70 (2H, m), 3.40 (3H, d, J = 14.3 Hz), 2.76 (1H, s), 2.59 (3H, s), 2.35-2.08 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 507, Found 507. Anal. ($C_{26}H_{23}N_4O_4SF$•$0.4CH_2Cl_2$) C, H, N.

Example 5(p): 4-Fluoro-5-[2-((R)-3-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 5(p) was prepared in a similar manner as Example 4(n) except that Example 5(o) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (1H, d, J = 5.4 Hz), 7.83 (1H, d, J = 17.3 Hz), 7.46 (1H, d, J = 8.9 Hz), 7.08 (1H, d, J = 7.5 Hz), 6.58 (1H, d, J = 5.4 Hz), 6.40 (1H, s), 4.51-4.38 (br s, 1H), 4.12 (2H, d, J = 2.5 Hz), 4.05-3.88 (2H, m), 3.79-3.57 (3H, m), 2.64 (1H, s), 2.47 (3H, s), 2.16-1.98 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 493, found 493. Anal. ($C_{25}H_{21}N_4O_4SF$•$0.2CH_2Cl_2$) C, H, N.

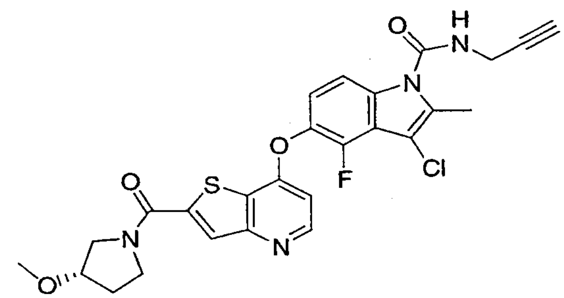
Step i: 5-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-methoxy-pyrrolidine-1-carbonyl]-thieno[3,2-b]pyridin-7-yloxy}-2-methyl-indole-1-carboxylic acid methylamide.



To a 2 mL of methlyene chloride was added [2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-methoxy-pyrrolidin-1-yl]-[7-(2-methyl-1H-indol-5-yloxy)-thieno[3,2-b]pyridin-2-yl]-methanone (0.15g, 0.26 mmol), NaOH (0.032 g, 0.82 mmol), Tetrabutyl-ammonium bromide (0.01g. 0.028 mmol) and methylisocynate (0.0.62g, 1.08 mmol). After stirring for 3h, the reaction mixture was partitioned between EtOAc (50 mL) and saturated $NaHCO_3$ (2 X 50 mL). The organic layer was dried over $NaSO_4$ and concentrated. The residue was purified using 2 mm chromatotron rotor eluting with EtOAc/CH_2Cl_2 (1:1) purified fraction concentrated to give 0.12 g (74%) of 5-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-methoxy-pyrrolidine-1-carbonyl]-thieno[3,2-b]pyridin-7-yloxy}-2-methyl-indole-1-carboxylic acid methylamide as clear oil. HPLC: R_t 5.02 min. (98 % area). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.48 (1H, d, J = 5.5 Hz), 7.81 (1H, s), 7.36 (1H, bd, J = 4.5), 7.75 (1H,

s), 7.30-7.25 (2H, m), 7.04 (1H, d, J = 7.4 Hz), 6.56 (1H, q, J = 5.5 Hz), 6.39 (1H, s), 4.51 (1H, bs), 4.17-4.06 (3H, m), 3.83-3.77 (1H, m), 3.65 (1H, d, J = 10.1 Hz), 3.24 (3H, S), 3.19 (3H, s), 2.96 (3H, d, J = 4.4 Hz), 2.48 (3H, s), 2.31-2.24 (1H, m), 2.15-2.10 (1H, m), 0.97 (9H, s). ACPI LCMS (M + H^+) *m/z*: 609.2.

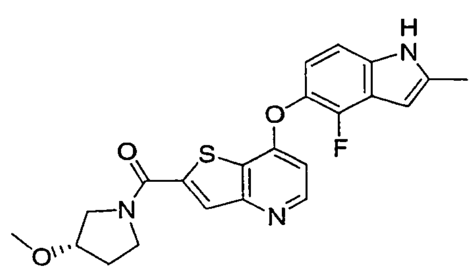
Example 6(a): 3-Chloro-4-fluoro-5-[2-(3S-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 6(a) was prepared in a similar manner as Example 4(a) except that propargylamine was used instead of methylamine and 3-Chloro-4-fluoro-5-[2-(3-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid 4-nitro-phenyl ester, prepared as described below, was used intead of 2-methyl-5-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1-(4-nitrophenoxy)indole. ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (1H, d, *J* = 5.5 Hz), 7.93 (1H, d, *J* = 5.1 Hz), 7.61 (1H, d, *J* = 9.0 Hz), 7.24 (1H, dd, *J* = 8.8, 1.3 Hz), 6.71 (1H, d, *J* = 5.5 Hz), 4.24 (2H, d, *J* = 2.4 Hz), 4.20-3.88 (3H, m), 3.85-3.66 (2H, m), 3.49 (3H, d, *J* = 13.9 Hz), 2.79-2.74 (1H, m), 2.54 (3H, s), 2.38-2.08 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 541, found 541. Anal. ($C_{26}H_{22}N_4O_4SFCl{\bullet}0.3CH_2Cl_2$) C, H, N.

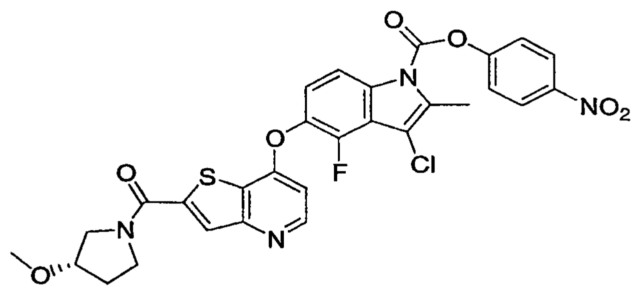
The starting materials were prepared as follows:

(i) [7-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-thieno[3,2-*b*]pyridin-2-yl]-(3S-methoxy-pyrrolidin-1-yl)-methanone



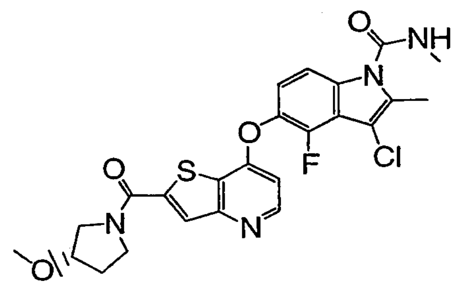
The title compound was prepared in a similar manner as Example 5(a) except that 3S-methoxy-pyrrolidine was used instead of 2S-methoxymethyl-pyrrolidine in the referenced step (i) of Example 4(a). ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (d, 1H, J = 5.5 Hz), 8.02 (d, 1H, J = 9.2 Hz), 7.82 (d, 1H, J = 5.5 Hz), 7.09 (d, 1H, J = 8.7 Hz), 6.93 (dd, 1H, J = 8.7, 1.5 Hz), 6.77 (d, 1H, J = 9.2 Hz), 6.46 (s, 1H), 4.05-3.78 (m, 2H), 3.73-3.55 (m, 2H), 3.29 (d, 3H, J = 14.1 Hz), 2.29 (s, 3H), 2.20-1.95 (m, 2H). LCMS (ESI+) [M+H]/z Calc'd 426, found 426.

(ii) 3-Chloro-4-fluoro-5-[2-(3-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid 4-nitro-phenyl ester



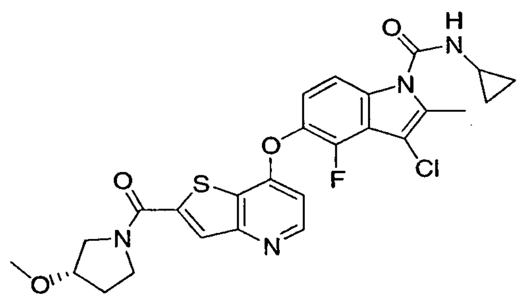
To a stirred solution of [7-(4-Fluoro-2-methyl-1h-indol-5-yloxy)-thieno[3,2-b]pyridin-2-yl]-(3-methoxy-pyrrolidin-1-yl)-methanone (399 mg, 0.94mmole) in CH_2Cl_2 (30 ml) and DMSO (0.2 ml) were added, sequentially, freshly crushed NaOH (700 mg, 17.50 mmole), Bu_4NBr (25 mg, catalytic amount) and 4-nitrophenyl chloroformate (1.18 g, 5.84 mmole). After stirring at ambient temperature for overnight, the reaction mixture was filtered and the filtrate was concentrated, *in vacuo*, to give crude product, which was further purified by flash column chromatography eluted with EtOAc : CH_2Cl_2 : MeOH (1:1:0.02) to provide 110 mg (19%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (1H, d, J = 5.5 Hz), 8.40 (2H, d, J = 8.7 Hz), 8.04 (1H, d, J = 9.1 Hz), 7.86 (1H, d, J = 10.7 Hz), 7.53 (2H, d, J = 9.04 Hz), 7.26 (1H, dd, J = 9.2, 1.9 Hz), 6.62 (1H, d, J = 5.5 Hz), 4.02-3.89 (3H, m), 3.88-3.71 (2H, m), 3.37 (3H, d, J = 15.1 Hz), 2.73 (3H, s), 2.29-2.08 (2H, m).

Example 6(b): 3-Chloro-4-fluoro-5-[2-(3S-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



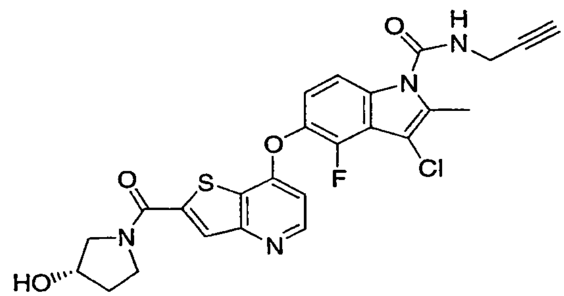
Example 6(b) was prepared in a similar manner as Example 6(a) except that methylamine was used instead of propargylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (1H, d, J = 5.5 Hz), 7.98 (1H, d, J = 5.2 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.13 (1H, dd, J = 8.3, 0.2 Hz), 6.61 (1H, d, J = 5.5 Hz), 4.09-3.82 (3H, m), 3.76-3.54 (2H, m), 3.29 (3H, d, J = 14.3 Hz), 2.92 (3H, s), 2.44 (3H, s), 2.30-2.04 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 517, found 517. Anal. ($C_{24}H_{22}N_4O_4SFCl{\bullet}0.5CH_2Cl_2$) C, H, N.

Example 6(c): 3-Chloro-4-fluoro-5-[2-(3S-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropyl- amide



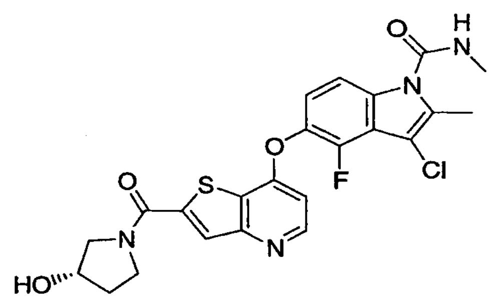
Example 6(c) was prepared in a similar manner as Example 6(a) except that cyclopropylamine was used instead of propargylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (1H, d, J = 5.5 Hz), 7.98 (1H, d, J = 6.2 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.26 (1H, dd, J = 8.7, 0.1 Hz), 6.73 (1H, d, J = 6.0 Hz), 4.19-4.01 (3H, m), 3.82-3.68 (2H, m), 3.40 (3H, d, J = 14.2 Hz), 2.95-2.86 (1H, m), 2.53 (3H, s), 2.30-2.04 (2H, m), 0.93-0.87 (2H, m), 0.79-0.70 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 543, found 543. Anal. ($C_{26}H_{24}N_4O_4SFCl{\bullet}0.3CH_2Cl_2$) C, H, N.

Example 6(d): 3-Chloro-4-fluoro-5-[2-(3S-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



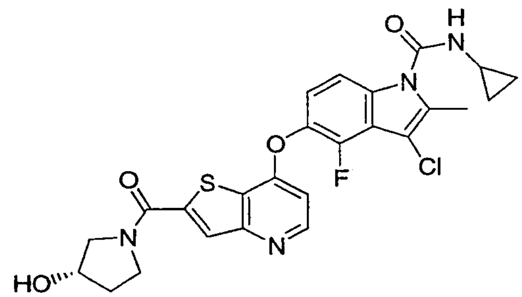
Example 6(d) was prepared in a similar manner as Example 4(n) except that Example 6(a) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (1H, d, J = 5.5 Hz), 7.79 (1H, d, J = 5.1 Hz), 7.63 (1H, d, J = 8.8 Hz), 7.27 (1H, dd, J = 8.8, 1.3 Hz), 6.74 (1H, d, J = 5.5 Hz), 6.40 (1H, s), 4.25 (2H, d, J = 2.6 Hz), 4.12-3.76 (3H, m), 3.86-3.74 (2H, m), 2.78-2.74 (1H, m), 2.56 (3H, s), 2.23-2.00 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 527, found 527. Anal. ($C_{25}H_{20}N_4O_4SFCl$•1.0H_2O) C, H, N.

Example 6(e): 3-Chloro-4-fluoro-5-[2-(3S-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



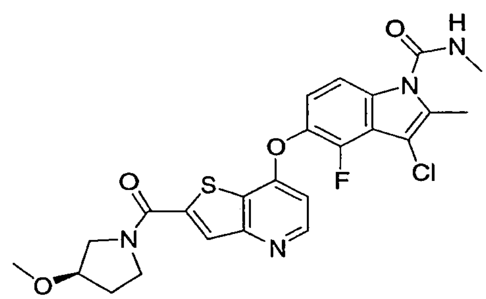
Example 6(e) was prepared in a similar manner as Example 4(n) except that Example 6(b) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (1H, d, J = 5.6 Hz), 7.84 (1H, d, J = 17.1 Hz), 7.47 (1H, d, J = 9.0 Hz), 7.13 (1H, dd, J = 8.7, 1.1 Hz), 6.60 (1H, d, J = 5.5 Hz), 4.41 (1H, bs), 4.01-3.90 (2H, m), 3.73-3.63 (2H, m), 3.63-3.55 (1H, m), 2.91 (3H, s), 2.42 (3H, s), 2.09-1.92 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 503, found 503. Anal. ($C_{23}H_{20}N_4O_4SFCl$•0.2CH_2Cl_2) C, H, N.

Example 6(f): 3-Chloro-4-fluoro-5-[2-(3S-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyclopropyl- amide



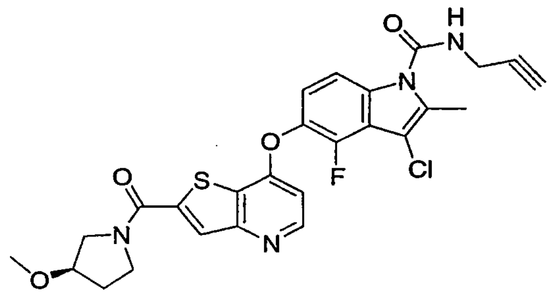
Example 6(f) was prepared in a similar manner as Example 4(n) except that Example 6(c) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.43 (1H, d, J = 5.6 Hz), 7.84 (1H, d, J = 17.1 Hz), 7.40 (1H, d, J = 9.0 Hz), 7.13 (1H, dd, J = 8.7, 1.1 Hz), 6.60 (1H, d, J = 5.5 Hz), 4.42 (1H, bs), 4.09-3.89 (2H, m), 3.74-3.65 (2H, m), 3.65-3.58 (1H, m), 2.83-2.77 (1H, m), 2.40 (3H, s), 2.10-1.89 (2H, m), 0.81-0.72 (2H, m), 0.66-0.61 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 529, found 529. Anal. ($C_{25}H_{22}N_4O_4SFCl$•$0.5CH_2Cl_2$) C, H, N.

Example 6(g): 3-Chloro-4-fluoro-5-[2-(3R-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



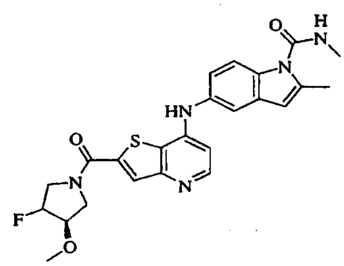
Example 6(g) was prepared in a similar manner as Example 6(b) except that 3R-methoxy-pyrrolidine instead of 3S-methoxy-pyrrolidine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (d, 1H, J = 5.5 Hz), 7.83 (d, 1H, J = 5.5 Hz), 7.45 (d, 1H, J = 9.0 Hz), 7.02 (dd, 1H, J = 8.7, 1.1 Hz), 6.59 (d, 1H, J = 5.5 Hz), 4.09-3.78 (m, 3H), 3.75-3.54 (m, 2H), 3.26 (d, 3H, J = 13.9 Hz), 2.92 (s, 3H), 2.42 (s, 3H), 2.23-1.93 (m, 2H). LCMS (ESI+) [M+H]/z Calc'd 517, found 517. Anal. ($C_{24}H_{22}N_4O_4SFCl$•0.4MeOH) C, H, N.

Example 6(h): 3-Chloro-4-fluoro-5-[2-((R)-3-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



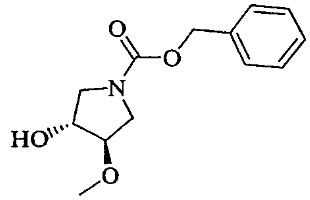
Example 6(h) was prepared in a similar manner as Example 6(g) except that propargylamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.65 (1H, d, J = 5.5 Hz), 7.97 (1H, d, J = 5.7 Hz), 7.63 (1H, d, J = 8.9 Hz), 7.26 (1H, dd, J = 1.1, 8.9 Hz), 6.74 (1H, d, J = 5.5 Hz), 4.25 (2H, d, J = 2.5 Hz), 4.17-3.91 (3H, m), 3.86-3.70 (2H, m), 3.40 (3H, d, J = 14.1 Hz), 2.74 (1H, s), 2.56 (3H, s), 2.34-2.06 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 541, Found 541. Anal. ($C_{26}H_{22}N_4O_4SFCl\bullet0.5CH_2Cl_2$) C, H, N.

Example 7(a): 5-[(2-{[(4*R*)-3-Fluoro-4-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)amino]-*N*,2-dimethyl-1*H*-indole-1-carboxamide



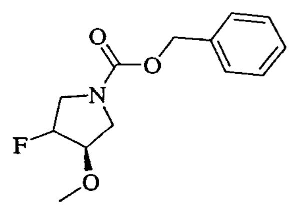
Example 7(a) was prepared in a similar manner as Example 2(a) except that 7-Chloro-2-{[(4*R*)-3-fluoro-4-methoxypyrrolidin-1-yl]carbonyl}thieno [3,2-*b*]pyridine, prepared as described below, was used instead of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine. ^{1}H NMR (CD_3OD) δ 8.13 (1H, d, J = 5.7 Hz), 7.69 (1H, d, J = 6.8 Hz), 7.57 (1H, d, J = 8.6 Hz), 7.30 (1H, d, J = 1.9 Hz), 7.04 (1H, dd, J = 1.9, 8.6 Hz), 6.66 (1H, d, J = 5.7 Hz), 6.52 (1H, s), 5.24-5.03 (1H, m), 4.06-3.95 (4H, m), 3.77-3.73 (1H, m), 3.33 (3H, d, J = 15.3 Hz), 2.91 (3H, s), 2.44 (3H, s). Anal. Calc'd for $C_{24}H_{24}FN_5O_3S\bullet0.45CH_3OH$: C, 59.21; H, 5.24; N, 14.12; found: C, 59.76; H, 5.27; N, 13.76. ESIMS (MH^+): 482.15.

Step (i) Benzyl (3*R*, 4*R*)-3-hydroxy-4-methoxypyrrolidine-1-carboxylate



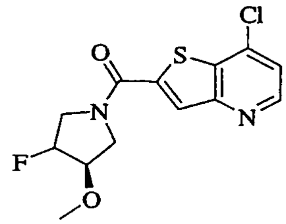
To a solution of benzyl (3*R*, 4*R*)-3,4-dihydroxypyrrolidine-1-carboxylate (3.81 g, 16.1 mmol) in 60 mL THF was added NaH (0.803 g, 20.07 mmol). The reaction mixture was stirred at room temperature for 15 min, CH_3I (2.0 mL, 32.2 mmol) was added and stirred at room temperature overnight. The reaction mixture was quenched with H_2O (80 mL) and extracted with EtOAc (2x100 mL). The organic layer was dried and concentrated. The residue was purified by flash column chromatography (1~2 % CH_3OH in CH_2Cl_2) to give a white solid (1.12 g, 28%). ^{1}H NMR ($CDCl_3$) δ 7.36-7.29 (5H, m), 5.12 (2H, s), 4.28-4.27 (1H, m), 3.72-3.37 (5H, m), 3.35 (3H, s), 1.95-1.89 (1H, m). ESIMS (MH^+): 252.05.

Step (ii) Benzyl (4*R*)-3-fluoro-4-methoxypyrrolidine-1-carboxylate



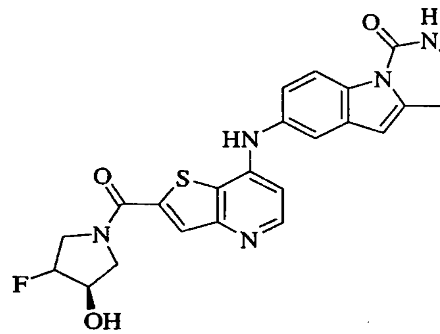
To a solution of benzyl (3*R*, 4*R*)-3-hydroxy-4-methoxypyrrolidine-1-carboxylate (0.818 g, 3.26 mmol) in 20 mL CH_2Cl_2 at –20 °C was added DAST (0.946 mL, 7.16 mmol). The reaction mixture was stirred at –20 °C and then room temperature overnight. The reaction mixture was quenched with 30 mL half saturated $NaHCO_3$, stirred at room temperature for 15 min and extracted with EtOAc (2x30 mL). The organic layer was dried and concentrated. The residue was purified by flash column chromatography (25% EtOAc in Hexane) to give pale yellow solid (0.551 g, 67%). ^{1}H NMR ($CDCl_3$) δ 7.36-7.29 (5H, m), 5.13 (2H, s), 5.09, 4.92 (1H, m), 3.95-3.91 (1H, m), 3.74-3.35 (4H, m), 3.37 (3H, s).

Step (iii) 7-Chloro-2-{[(4*R*)-3-fluoro-4-methoxypyrrolidin-1-yl]carbonyl}thieno [3,2-*b*]pyridine



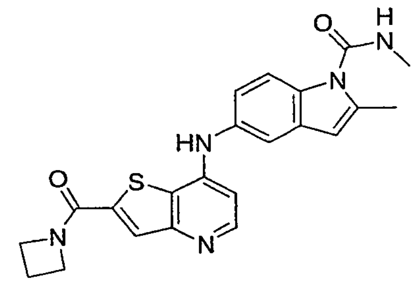
This material was prepared by the coupling of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate and (4*R*)-3-fluoro-4-methoxypyrrolidine in a manner as previously described for Example 1(a), step (iv). ^{1}H NMR (CD_3OD) δ 8.57 (1H, d, *J* = 5.1 Hz), 7.94 (1H, d, *J* = 7.2 Hz), 7.48 (1H, d, *J* = 5.1 Hz), 5.27-5.05 (1H, m), 4.18-3.93 (4H, m), 3.78-3.75 (1H, m), 3.35 (3H, d, *J* = 14.1 Hz). ESIMS (MH^+): 315.05

Example 7 (b): 5-[(2-{[(4*R*)-3-Fluoro-4-hydroxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)amino]-*N*,2-dimethyl-1*H*-indole-1-carboxamide



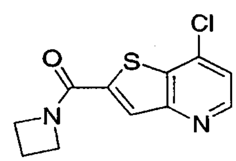
Example 7(b) was prepared in a similar manner as Example 4(n) except that 7(a) was used as starting material. ^{1}H NMR (CD_3OD) δ 8.13 (1H, d, *J* = 5.7 Hz), 7.70 (1H, s), 7.56 (1H, d, *J* = 8.7 Hz), 7.30 (1H, d, *J* = 2.0 Hz), 7.04 (1H, dd, *J* = 2.0, 8.7 Hz), 6.66 (1H, d, *J* = 5.7 Hz), 6.25 (1H, s), 5.06-4.81 (1H, m), 4.37-4.17 (1H, m), 4.11-3.63 (4H, m), 3.24 (3H, s), 2.91 (3H, s), 2.44 (3H, s). Anal. Calc'd for $C_{23}H_{22}FN_5O_3S \bullet 0.4CH_3OH \bullet 0.25CH_2Cl_2$: C, 56.63; H, 4.84; N, 13.96; Found: C, 56.98; H, 4.85; N, 13.70. ESIMS (MH^+): 468.20.

Example 7 (c): 5-[2-(Azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid methylamide



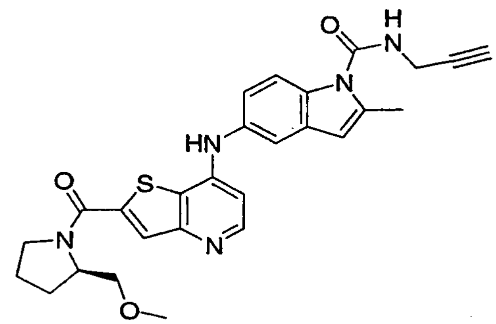
Example 7(c) was prepared in a similar manner as Example 2(a) except that 7-Chloro-2-([azetidin-1-yl]carbonyl)thieno [3,2-*b*]pyridine, prepared as described below, was used instead of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine. ^{1}H NMR (300 MHz, DMSO) δ 8.87 (1H, s), 8.30 (1H, d, *J* = 5.4 Hz), 8.22 (1H, d, *J* = 4.2 Hz), 7.68 (1H, s), 7.62 (1H, d, *J* = 8.7 Hz), 7.36 (1H, s), 7.09 (1H, d, *J* = 8.9 Hz), 6.72 (1H, d, *J* = 5.4 Hz), 6.36 (1H, s), 4.61-4.56 (2H, m), 4.13-4.05 (2H, m), 3.33 (3H, s), 2.87 (3H, s), 2.39-2.29 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 420, Found 420. Anal. ($C_{22}H_{21}N_5O_2S$•$0.2CH_2Cl_2$) C, H, N.

Step (i)7-Chloro-2-([azetidin-1-yl]carbonyl)thieno [3,2-*b*]pyridine



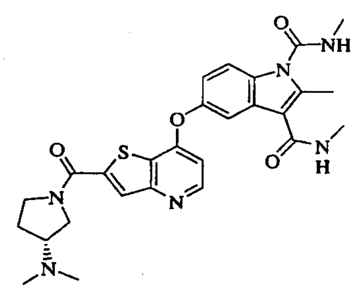
This material was prepared by the coupling of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate and azetidine in a manner as previously described for Example 1(a), step (iv). ^{1}H NMR (300 MHz, CD_3OD) δ 8.63 (1H, d, *J* = 5.6 Hz), 7.85 (1H, s), 7.54 (1H, d, *J* = 5.6 Hz), 4.74-4.62 (2H, m), 4.32-4.23 (2H, m), 2.58-2.49 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 253, Found 253.

Example 7 (d): 5-[2-(2R-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-ylamino]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



Example 7(d) was prepared in a similar manner as Example 1(b) except that propargylamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.21 (1H, d, J = 5.6 Hz), 7.74 (1H, s), 7.70 (1H, d, J = 8.8 Hz), 7.39 (1H, d, J = 2.0 Hz), 7.14 (1H, dd, J = 2.0, 8.8 Hz), 6.76 (1H, d, J = 5.6 Hz), 6,35 (1H, s), 4.41 (1H, m), 4.21 (2H, d, J = 2.5 Hz), 3.86 (2H, m), 3.60 (2H, m), 3.36 (3H, s), 2.72 (1H, t, J = 2.5 Hz), 2.54 (3H, s), 2.15-1.90 (4H, m). LCMS (ESI+) [M+H]/z Calc'd 502, Found 502.

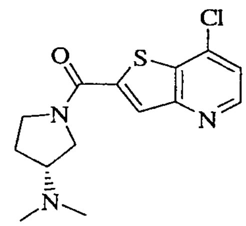
Example 8(a): 5-[(2-{[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}thieno[3,2-*b*] pyridin-7-yl)oxy]-*N*,*N*',2-trimethyl-1*H*-indole-1,3-dicarboxamide



To a solution of 2,2,6,6-tetramethylpiperidine (0.30 mmol, 0.051 mL) in THF cooled at 0 °C was added 1.6 M n-BuLi in hexane (0.30 mmol, 0.191 mL). The mixture was cooled to –78 °C and 5-[(2-{[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}thieno[3,2-*b*] pyridin-7-yl)oxy]-2-methyl-1*H*-indole-1,3-dicarboxamide (0.30 mmol, 0.126 g) in 2 mL THF was added dropwise. The reaction mixture was stirred at –78 °C for 5 min and methyl isocyanate (0.31 mmol, 0.018 g) was added. The reaction was stirred at -78 °C for 15 min and warmed to room temperature overnight. The reaction mixture was concentrated and partition between CH_2Cl_2 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (3-5% CH_3OH in CH_2Cl_2) to give pale yellow solid (0.064 g, 40%). ^{1}H NMR (CD_3OD) δ 8.39 (1H, d, J = 5.4 Hz), 7.82 (1H, d, J =

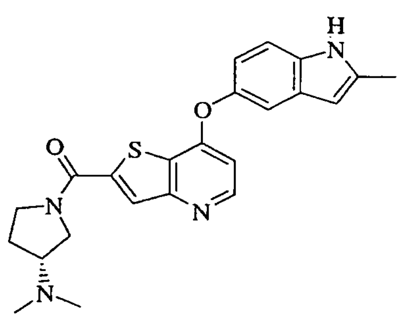
8.7 Hz), 7.37 (1H, d, J = 8.9 Hz), 7.28 (1H, d, J = 2.3 Hz), 6.99 (1H, dd, J = 2.3, 8.9 Hz), 6.59 (1H, d, J = 5.4 Hz), 4.09-3.96 (1H, m), 3.88-3.33 (3H, m), 3.14 (3H, s), 2.89-2.78 (1H, m), 2.70 (3H, s), 2.41 (3H, s), 2.25 (3H, s), 2.22 (3H, s), 2.21-2.19 (1H, m), 1.94-1.73 (1H, m). Anal. Calc'd for $C_{27}H_{30}N_6O_4S \bullet 0.3\ CH_2Cl_2$: C, 58.54; H, 5.51; N, 15.00; Found: C, 58.48; H, 5.59; N, 14.88. ESIMS (MH^+): 535.25.

Step (i): 7-Chloro-2-[3(*R*)-(dimethylamino)pyrrolidine-1-carbonyl]thieno[3,2-*b*]pyridine



HATU (4.99 g, 26.25 mmol) and Et_3N (7.23 mL, 52.50 mmol) was added to a solution of (3*R*)-*N*,*N*-dimethylpyrrolidin-3-amine (1.0 g, 17.5 mmol) and 7-chlorothieno[3,2-*b*] pyridine-2-carboxylic acid lithium salt (3.85 g, 17.5 mmol) in 30 mL DMF at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and solvent was concentrated. The residue was partition between H_2O and 10% CH_3OH in EtOAC. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (5-7% CH_3OH in CH_2Cl_2) to give a white solid (1.74 g, 32%). ^{1}H NMR (CD_3OD) δ 8.57 (1H, d, J = 5.2 Hz), 7.90 (1H, d, J = 7.9 Hz), 7.48 (1H, d, J = 5.2 Hz), 4.11-3.97 (1H, m), 3.90-3.36 (3H, m), 2.99-2.90 (1H, m), 2.30 (3H, s), 2.26 (3H, s), 1.97-1.72 (2H, m). ESIMS (MH^+): 310.10.

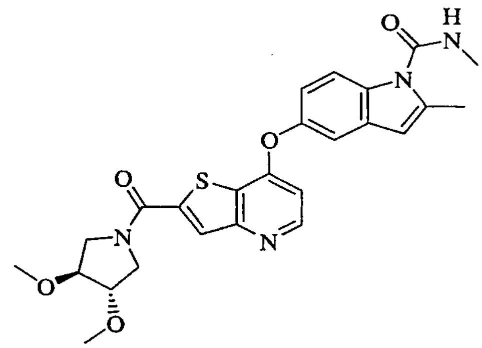
Step (ii): 5-(2-[3(*R*)-(dimethylamino)pyrrolidine-1-carbonyl]thieno[3,2-*b*]pyridin7-yloxy)-2-methyl-1*H*-indole



The title compound was prepared in a similar manner as Example 4(a), step (ii) except that 7-chloro-2-([3(*R*)-(dimethylamino)pyrrolidin-1-yl]carbonyl)thieno[3,2-*b*]pyridine was used instead of 7-chloro-2-[(*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-*b*]pyridine.

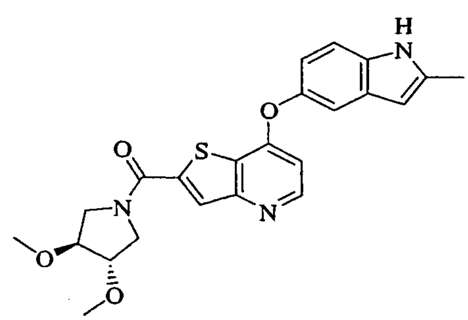
^{1}H NMR (CD_3OD) δ 8.34 (1H, d, J = 5.46 Hz), 7.79 (1H, d, J = 7.5 Hz), 7.24 (1H, d, J = 8.6 Hz), 7.15 (1H, d, J = 2.2 Hz), 6.76 (d1H, d, J = 2.2, 8.66 Hz), 6.55-6.52 (1H, m), 6.06 (1H, s), 4.07-3.94 (1H, m), 3.87-3.32 (3H, m), 2.89-2.79 (1H, m), 2.33 (3H, s), 2.25 (3H, s), 2.22 (3H, s), 2.21-2.12 (1H, m), 1.93-1.72 (1H, m). ESIMS (MH^+): 421.20.

Example 8 (b): 5-[(2-{[(3*S*,4*S*)-3,4-Dimethoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-dimethyl-1*H*-indole-1-carboxylic acid methylamide



Example 8(b) was prepared in a similar manner as Example 4(q) except that methylamine was used instead of propargylamine. ^{1}H NMR (CD_3OD) δ 8.38 (1H, d, J = 5.5 Hz), 7.82 (1H, s,), 7.63 (1H, d, J = 8.9 Hz), 7.23 (1H, d, J = 2.3 Hz), 6.94 (1H, dd, J = 2.3, 8.9 Hz), 6.57 (1H, d, J = 5.5 Hz), 6.28 (1H,s), 3.96-3.81 (4H, m), 3.66-3.65 (2H, m), 3.34 (3H, s), 3.29 (3H, s), 2.91 (3H, s), 2.45 (3H, s). Anal. Calc'd for $C_{25}H_{26}N_4O_5S$•0.4 CH_3OH: C, 60.12; H, 5.48; N, 11.04; Found: C, 60.46; H, 5.77; N, 10.90.

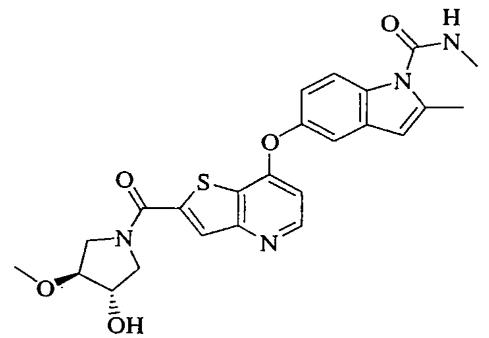
Step (i): 2-{[(3*S*,4*S*)-3,4-Dimethoxypyrrolidin-1-yl]carbonyl}-7-[(2-methyl-1*H*-indol-5-yl)oxy]thieno[3,2-*b*]pyridine



The title compound was prepared in a similar manner as Example 4(a), step (ii) except that 7-chloro-2-([3(*S*),4(*S*)-dimethoxypyrrolidin-1-yl]carbonyl)thieno[3,2-*b*]pyridine was used instead of 7-chloro-2-[(*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-

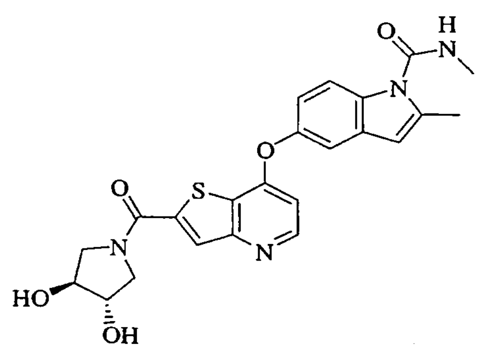
b]pyridine. ^{1}H NMR (CD_3OD) δ 8.35 (1H, d, *J* = 5.5 Hz), 7.81 (1H, s,), 7.25 (1H, d, *J* = 8.5 Hz), 7.16 (1H, d, *J* = 2.3 Hz), 6.77 (1H, dd, *J* = 2.3, 8.5 Hz), 6.54 (1H, d, *J* = 5.5 Hz), 6.07 (1H, s), 4.00-3.81 (4H, m), 3.72-3.65 (2H, m), 3.34 (3H, s), 3.29 (3H, s), 2.34 (3H, s). ESIMS (MH^+): 438.20.

Example 8 (c): 5-[(2-{[(3*S*,4*S*)-3-Hydroxy-4-methoxypyrrolidin-1-yl]carbonyl} thieno[3,2-*b*]pyridin-7-yl)amino]-*N*,2-dimethyl-1*H*-indole-1-carboxamide



Example 8(c) was prepared in a similar manner as Example 8(b) except that 3(*S*)-hydroxy-4(S)-methoxypyrrolidine was used in place of 3(S),4(S)-dimethoxypyrrolidine. ^{1}H NMR (CD_3OD) δ 8.38 (1H, br. s), 7.83 (1H, d, *J* = 9.42 Hz), 7.63 (1H, d, *J* = 8.9 Hz), 7.23 (1H, d, *J* = 2.3 Hz), 6.94 (1H, dd, *J* = 2.3, 8.9 Hz), 6.58 (1H, d, *J* = 5.5 Hz), 6.28 (1H, s), 4.29-4.22 (1H, m), 4.06-3.96 (1H, m), 3.83-3.54 (4H, m), 3.30 (3H, d, *J* = 14.0), 2.91 (3H, s), 2.45 (3H, s). HRMS Calc'd for $C_{24}H_{24}N_4O_5S$ [MH^+]: 481.1537; Found 481.1546.

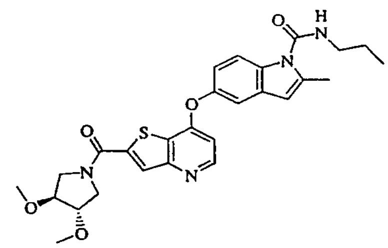
Example 8 (d): 5-[(2-{[(3*S*,4*S*)-3,4-Dihydroxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*] pyridin-7-yl)amino]-*N*,2-dimethyl-1*H*-indole-1-carboxamide



Example 8(d) was prepared in a similar manner as Example 4(n) except that 8(b) was used as

starting material. ^{1}H NMR (DMSO-d_6) δ 8.54 (1H, d, J = 5.4 Hz), 8.28 (1H, m), 8.03 (1H, s), 7.68 (1H, d, J = 8.9 Hz), 7.41 (1H, d, J = 2.3 Hz), 7.07 (1H, dd, J = 2.3, 8.9 Hz), 6.65 (1H, d, J = 5.4 Hz), 6.40 (1H, s), 5.27 (2H, m), 4.11-3.99 (4H, m), 3.71-3.65 (2H, m), 3.32 (3H, s), 2.87 (3H, s). HRMS Calc'd for $C_{23}H_{22}N_4O_5S$ [MH+]: 467.1390; Found: 467.1389.

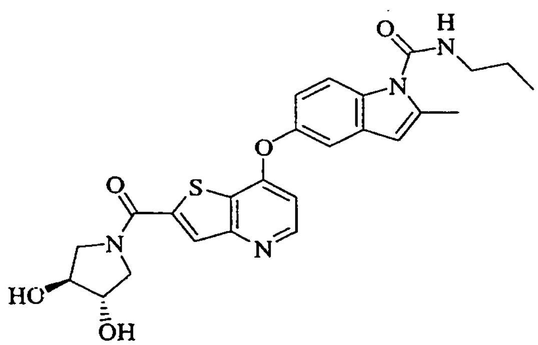
Example 8 (e): 5-[(2-{[(3*S*,4*S*)-3,4-dimethoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methyl-*N*-propyl-1*H*-indole-1-carboxamide



Example 8(e) was prepared in a similar manner as Example 8(b) except that propylamine was used instead of methylamine. ^{1}H NMR (CD_3OD) δ 8.38 (1H, d, J = 5.5Hz), 7.82 (1H, s), 7.61 (1H, d, J = 8.9 Hz), 7.24 (1H, d, J = 2.3 Hz), 6.95 (1H, dd, J = 2.3, 8.9 Hz), 6.57 (1H, d, J = 5.5 Hz), 6.29 (1H, s), 4.00-3.81 (4H, m), 3.73-3.65 (2H, m), 3.34 (3H, s), 3.29 (3H, s), 3.30-3.24 (2H, m), 2.45 (3H, s), 1.69-1.57 (2H, m), 0.95 (3H, t, J = 7.4 Hz).

Anal. Calc'd for $C_{27}H_{30}N_4O_5S{\bullet}0.4H_2O$: C, 61.21; H, 5.86; N, 10.58; Found: C, 60.85; H, 6.03; N, 10.90. ESIMS (MH^+): 523.20.

Example 8 (f): 5-[(2-{[(3*S*,4*S*)-3,4-Dihydroxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methyl-*N*-propyl-1*H*-indole-1-carboxamide

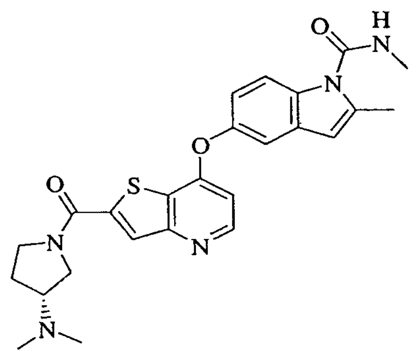


Example 8(f) was prepared in a similar manner as Example 8(d) except that propylamine was used instead of methylamine. ^{1}H NMR (DMSO-d_6) δ 8.54 (1H, d, J = 5.5 Hz), 8.44-8.41 (1H,

m), 8.03 (1H, s), 7.65 (1H, d, J = 8.9 Hz), 7.41 (1H, d, J = 2.3 Hz), 7.08 (1H, dd, J = 2.3, 8.9 Hz), 6.65 (1H, d, J = 5.5 Hz), 6.40 (1H, s), 5.29-5.25 (2H, m), 4.11-3.99 (4H, m), 3.71-3.65 (2H, m), 3.42-3.24 (5H, m), 1.69-1.57 (2H, m), 0.95 (3H, t, J = 7.4 Hz).

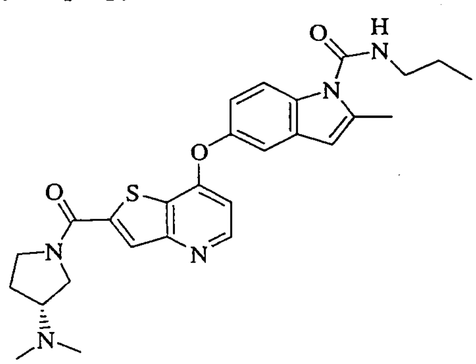
HRMS Calc'd for $C_{25}H_{26}N_4O_5S$ [MH^+]: 495.1702; Found: 495.1702.

Example 8 (g): 5-[(2-{[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}thieno[3,2-*b*] pyridin-7-yl)oxy]-*N*,2-dimethyl-1*H*-indole-1-carboxamide



Example 8(g) was prepared in a similar manner as Example 8(b) except that 3(*R*)-(dimethylamino)pyrrolidine was used in place of 3(S),4(S)-dimethoxypyrrolidine. ^{1}H NMR (CD_3OD) δ 8.38 (1H, d, J = 5.5 Hz), 7.81 (1H, d, J = 7.5 Hz), 7.63 (1H, d, J = 8.9 Hz), 7.23 (1H, d, J = 2.2 Hz), 6.94 (1H, dd, J = 2.2, 8.9 Hz), 6.58 (1H, d, J = 5.5 Hz), 6.28 (1H, s), 4.08-3.74 (3H, m), 3.61-3.35 (2H, m), 2.91 (3H, s), 2.45 (3H, s), 2.25 (3H, s), 2.22 (3H, s), 1.93-1.74 (2H, m). HRMS Calc'd for $C_{25}H_{27}N_5O_3S$ [MH^+]: 478.1934; Found: 478.1913.

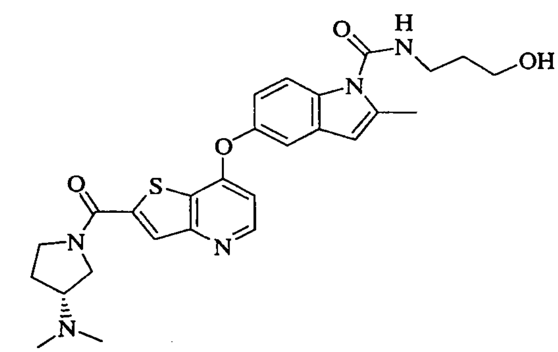
Example 8 (h): 5-[(2-{[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}thieno[3,2-*b*] pyridin-7-yl)oxy]-2-methyl-*N*-propyl-1*H*-indole-1-carboxamide



Example 8(h) was prepared in a similar manner as Example 8(d) except that propylamine was

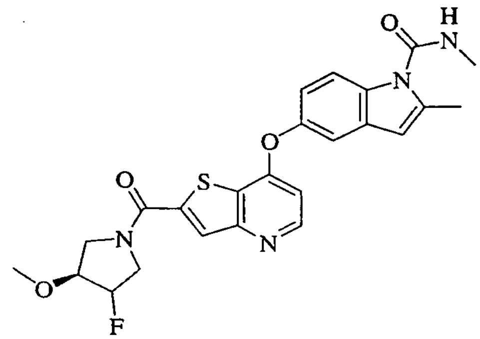
used instead of methylamine. ^{1}H NMR (CD_3OD) δ 8.37 (1H, d, J = 5.5 Hz), 7.80 (1H, d, J = 8.1 Hz), 7.60 (1H, d, J = 8.9 Hz), 7.23 (1H, d, J = 2.3 Hz), 6.94 (1H, dd, J = 2.3, 8.9 Hz), 6.56 (1H, d, J = 5.5 Hz), 6.27 (1H, s), 4.07-3.95 (1H, m), 3.86-3.73 (1H, m), 3.60-3.49 (1H, m), 3.39-3.14 (m,3H), 2.87-2.80 (1H, m), 2.45 (3H, s), 2.24 (3H, s), 2.21 (3H, s), 1.93-1.75 (1H, m), 1.62 (2H, q, J = 7.2 Hz), 1.34-1.25 (1H, m), 0.95 (3H, t, J = 7.2 Hz). HRMS Calc'd for $C_{27}H_{31}N_5O_3S$ [MH+]: 506.2216; Found: 506.2226.

Example 8 (i): 5-[(2-{[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}thieno[3,2-*b*] pyridin-7-yl)oxy]-*N*-(3-hydroxypropyl)-2-methyl-1*H*-indole-1-carboxamide



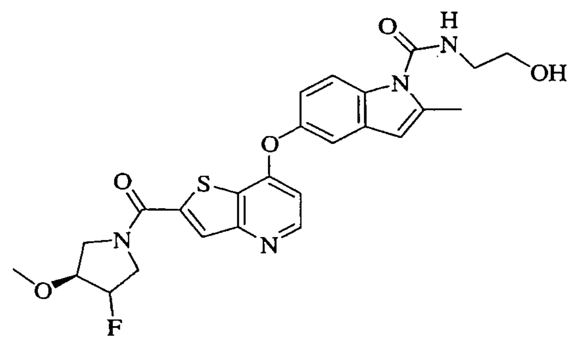
Example 8(i) was prepared in a similar manner as Example 8(d) except that 3-aminopropan-1-ol was used instead of methylamine. ^{1}H NMR (CD_3OD) δ 8.37 (1H, d, J = 5.5 Hz), 7.81 (1H, d, J = 8.9 Hz), 7.64 (1H, d, J = 8.9 Hz), 7.24 (1H, d, J = 2.5 Hz), 6.94 (1H, dd, J = 2.5, 8.9 Hz), 6.57 (1H, d, J = 5.5 Hz), 6.29 (1H, s), 4.08-3.95 (1H, m), 3.87-3.74 (2H, m), 3.64-3.51 (3H, m), 3.47-3.36 (3H, m), 2.88-2.81 (1H, m), 2.46 (3H, s), 2.25 (3H, s), 2.22 (3H, s), 1.90-1.78 (3H, m). Anal Calc'd for $C_{27}H_{21}N_5O_4S{\bullet}1.2H_2O$: C, 59.69; H, 6.20; N, 12.89; Found: C, 60.13; H, 6.17; N, 12.38.

Example 8 (j): 5-[(2-{[(4*S*)-3-Fluoro-4-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*] pyridin-7-yl)oxy]-*N*,2-dimethyl-1*H*-indole-1-carboxamide



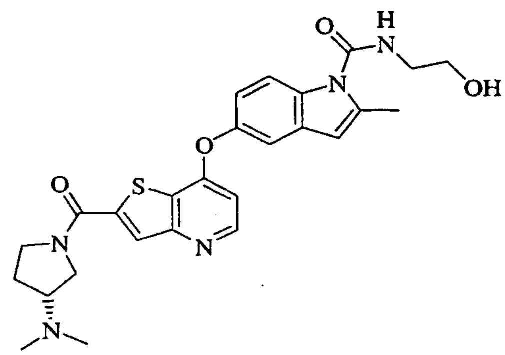
Example 8(j) was prepared in a similar manner as Example 8(b) except that 3-fluoro-4(S)-methoxypyrrolidine was used in place of 3(S),4(S)-dimethoxypyrrolidine. ^{1}H NMR (CD_3OD) δ 8.38 (1H, d, J = 5.5 Hz), 7.84 (1H, d, J = 6.8 Hz), 7.62 (1H, d, J = 8.9 Hz), 7.24 (1H, d, J = 2.3 Hz), 6.94 (1H, dd, J = 2.3, 8.96 Hz), 6.58 (1H, d, J = 5.5 Hz), 6.28 (1H, s), 5.26-5.21 (m, 0.5H), 5.09-5.04 (m, 0.5H), 4.15-3.68 (5H, m), 3.32 (3H, d, J = 14.5 Hz), 2.91 (3H, m), 2.45 (3H, s). Anal. Calc'd for $C_{24}H_{23}FN_4O_4S$: C, 59.74; H, 4.80; N, 11.61; Found: C, 59.89; H, 5.03; N, 11.34. ESIMS (MH^+): 483.05.

Example 8 (k): 5-[(2-{[(4*S*)-3-Fluoro-4-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-*N*-(2-hydroxyethyl)-2-methyl-1*H*-indole-1-carboxamide



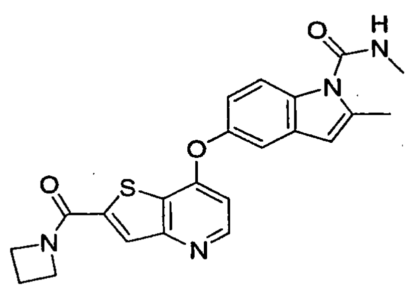
Example 8 (k) was prepared in a similar manner as Example 8(j) except that ethanolamine was used instead of methylamine. ^{1}H NMR (CD_3OD) δ 8.38 (1H, d, J = 5.5 Hz), 7.68 (1H, d, J = 8.9 Hz), 7.62 (1H, d, J = 8.9 Hz), 7.24 (1H, d, J = 2.5 Hz), 6.96 (1H, dd, J = 2.5, 8.9 Hz), 6.56 (1H, d, J = 5.5 Hz), 6.28 (1H, s), 5.26-5.21 (m, 0.5H), 5.09-5.04 (m, 0.5H), 4.08-3.23 (5H, m), 3.69-3.66 (2H, m), 3.43-3.35 (2H, m), 3.32 (3H, d, J = 14.7Hz), 2.45 (3H, s). Anal. Calc'd for $C_{25}H_{25}FN_4O_5S$: C, 58.58; H, 4.92; N, 10.93; Found: C, 58.50; H, 5.05; N, 10.61. ESIMS (MH^+): 513.10.

Example 8 (l): 5-[(2-{[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-*N*-(2-hydroxyethyl)-2-methyl-1*H*-indole-1-carboxamide



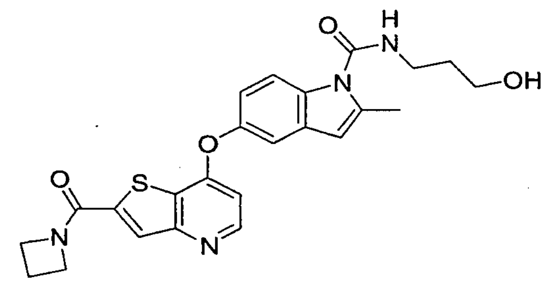
Example 8(l) was prepared in a similar manner as Example 8(d) except that ethanolamine was used instead of methylamine. ^{1}H NMR (CD$_3$OD) δ 8.37 (1H, d, J = 5.4 Hz), 7.81 (1H, d, J = 7.9 Hz), 7.72 (1H, d, J = 8.9 Hz), 7.23 (1H, d, J = 2.3 Hz), 6.94 (1H, dd, J = 2.3, 8.9 Hz), 6.57 (1H, d, J = 5.4 Hz), 6.28 (1H, s), 4.06-3.96 (1H, m), 3.87-3.77 (2H, m), 3.70 (2H, t, J = 5.7 Hz), 3.57-3.37 (4H, m), 2.91-2.79 (1H, m), 1.94-1.76 (1H, m). HRMS Calc'd for $C_{26}H_{29}N_5O_4S$ [MH+]: 508.2026; Found: 508.2019.

Example 8 (m): 5-[2-(Azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



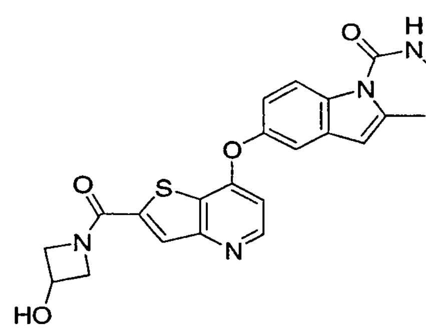
Example 8(m) was prepared in a similar manner as Example 8(b) except that azetidine was used in place of 3(S),4(S)-dimethoxypyrrolidine. ^{1}H NMR (300 MHz, DMSO) δ 8.56 (1H, d, J = 4.3 Hz), 8.30 (1H, d, J = 8.3 Hz), 7.90 (1H, s), 7.70 (1H, d, J = 8.9 Hz), 7.43 (1H, s), 7.09 (1H, d, J = 10.4 Hz), 6.66 (1H, d, J = 5.3 Hz), 6.42 (1H, s), 4.68-4.61 (2H, m), 4.15-4.10 (2H, m), 3.35 (3H, s), 2.90 (3H, s) 2.42-2.30 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 421, Found 421. Anal. ($C_{22}H_{20}N_4O_3S$) C, H, N.

Example 8 (n): 5-[2-(Azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (3-hydroxy-propyl)-amide



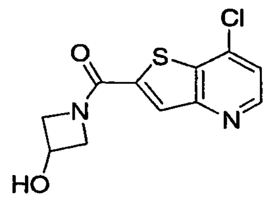
Example 8(n) was prepared in a similar manner as Example 8(m) except that 3-aminopropan-1-ol was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.49 (1H, d, *J* = 5.5 Hz), 7.81 (1H, s), 7.76 (1H, d, *J* = 8.9 Hz), 7.35 (1H, s), 7.06 (1H, d, *J* = 11.7 Hz), 6.70 (1H, d, *J* = 5.5 Hz), 6.40 (1H, s), 4.73-4.68 (2H, m), 4.33-4.22 (2H, m), 3.79-3.73(2H, m), 3.62-3.55 (2H, m), 2.58 (3H, s) 2.55-2.45 (2H, m), 1.97-1.90 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 465, Found 465. Anal. ($C_{24}H_{24}N_4O_4S$•$0.1CH_2Cl_2$) C, H, N.

Example 8 (o): 5-[2-(3-Hydroxy-azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



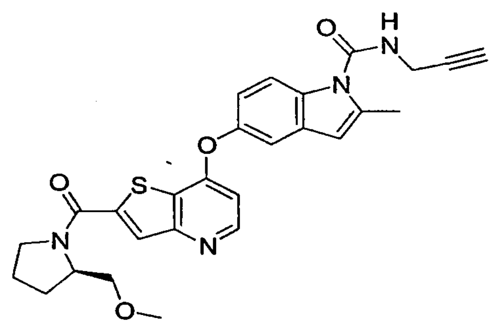
Example 8(o) was prepared in a similar manner as Example 8(b) except that 3-hydroxyazetidine was used in place of 3(S),4(S)-dimethoxypyrrolidine. ^{1}H NMR (300 MHz, DMSO) δ 8.86 (1H, s), 8.27 (1H, d, *J* = 5.5 Hz), 7.69 (1H, d, *J* = 4.5 Hz), 7.60 (1H, d, *J* = 8.7 Hz), 7.35 (1H, s), 7.08 (1H, d, *J* = 10.4 Hz), 6.70 (1H, d, *J* = 5.5 Hz), 6.36 (1H, s), 5.84 (1H, d, *J* = 6.2 Hz), 4.79-4.73 (1H, m), 4.61-4.52 (1H, m), 4.33-4.28(2H, m), 3.83-3.79 (1H, m), 2.87 (3H, d, *J* = 3.4 Hz). LCMS (ESI+) [M+H]/z Calc'd 436, Found 436. Anal. ($C_{22}H_{21}N_5O_3S$•$0.8CH_2Cl_2$) C, H, N.

Step (i) 7-Chloro-2-[3-hydroxyazetidin-1-yl)carbonyl]thieno[3,2-b]pyridine



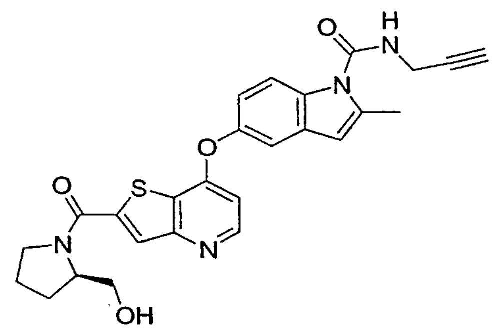
This material was prepared by the coupling of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate and 3-hydroxyazetidine in a manner as previously described for Example 1(a), step (iv). ^{1}H NMR (300 MHz, DMSO) δ 8.76 (1H, d, J = 5.1 Hz), 8.01 (1H, s), 7.72 (1H, d, J = 5.1 Hz), 5.92(1H, d, J = 6.4 Hz), 4.83-4.76 (1H, m), 4.64-4.56 (1H, m), 4.37-4.29 (2H, m), 3.86-3.72 (1H, m). LCMS (ESI+) [M+H]/z Calc'd 269, Found 269.

Example 8 (p): 5-[2-(2R-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



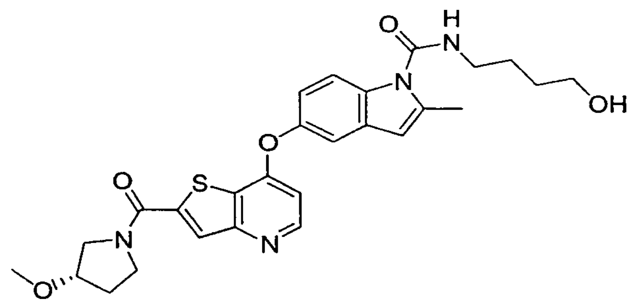
Example 8(p) was prepared in a similar manner as Example 4(e) except that propargylamine was used instead of methylamine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (1H, d, J = 5.5 Hz), 7.81 (1H, s), 7.76 (1H, d, J = 8.9 Hz), 7.24 (1H, d, J = 2.4 Hz), 7.00 (1H, dd, J = 2.4, 8.9 Hz), 6.53 (1H, d, J = 5.5 Hz), 6.33 (1H, d, J = 5.5 Hz), 6.30 (1H, s), 4.46 (1H, m), 4.30 (2H, m), 3.83 (2H, m), 3.62 (2H, m), 3.36 (3H, s), 2.59 (3H, s), 2.35 (1H, m), 2.20-1.85 (4H, m). LCMS (ESI+) [M+H]/z Calc'd 503, Found 503.

Example 8 (q): 5-[2-(2R-Hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



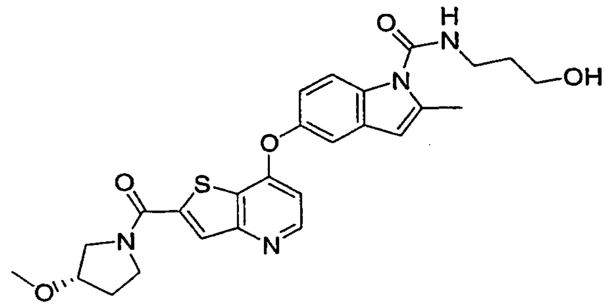
Example 8(q) was prepared in a similar manner as Example 4(n) except that 8(p) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.47 (1H, d, J = 5.67 Hz), 7.90 (1H, s), 7.77 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 2.2 Hz), 7.05 (1H, dd, J = 2.2, 8.8 Hz), 6.67 (1H, d, J = 5.6 Hz), 6.39 (1H, s), 4.35 (1H, m), 4.21 (2H, d, J = 2.5 Hz), 3.95-3.70 (4H, m), 2.72 (1H, t, J = 2.5 Hz), 2.56 (3H, s), 2.20-1.90 (4H, m). LCMS (ESI+) [M+H]/z Calc'd 489, Found 489.

Example 9 (a): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (4-hydroxy-butyl)-amide



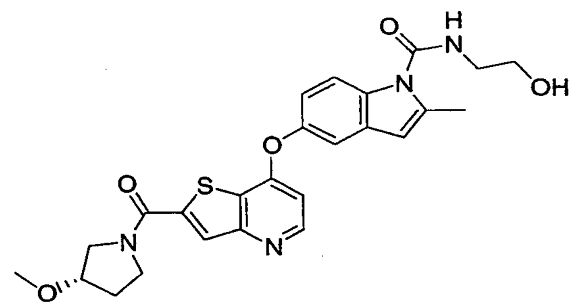
Example 9(a) was prepared in a similar manner as Example 4(g) except that 4-aminobutan-1-ol was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.46 (1H, d, J = 5.4 Hz), 7.89 (1H, d, J = 5.6 Hz), 7.71 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 2.1 Hz), 7.03 (1H, dd, J = 2.2, 8.8 Hz), 6.65 (1H, d, J = 5.5 Hz), 6.37 (1H, s), 4.13-3.70 (5H, m), 3.63 (2H, t, J = 6.2 Hz), 3.46 (2H, t, J = 6.8 Hz), 3.38, 3.33 (3H, s), 2.55 (3H, s), 2.25-2.05 (2H, m), 1.80-1.63 (4H, m). LCMS (ESI+) [M+H]/z Calc'd 523, Found 523. Anal. ($C_{27}H_{30}N_4O_5S$•$0.2H_2O$• 0.2Hexanes) C, H, N.

Example 9 (b): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (3-hydroxy-propyl)-amide



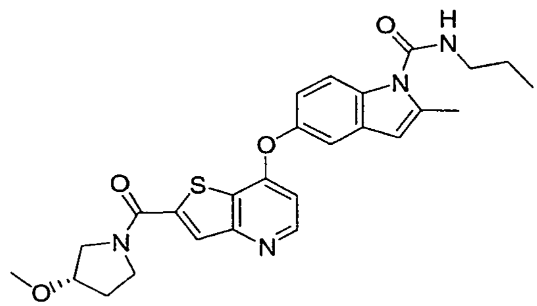
Example 9(b) was prepared in a similar manner as Example 4(g) 3-aminopropan-1-ol was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.48 (1H, d, J = 5.4 Hz), 7.91 (1H, d, J = 6.4 Hz), 7.74 (1H, d, J = 8.8 Hz), 7.34 (1H, d, J = 2.3 Hz), 7.05 (1H, dd, J = 2.4, 8.8Hz), 6.67 (1H, d, J = 5.4 Hz), 6.39 (1H, s), 4.15-3.70 (5H, m), 3.72 (2H, t, J = 6.2 Hz), 3.54 (2H, t, J = 6.9 Hz), 3.38, 3.34 (3H, s), 2.56 (3H, s), 2.15 (2H, m), 1.92 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 509, Found 509. Anal. ($C_{26}H_{28}N_4O_5S$•$0.5H_2O$•0.3Hexanes) C, H, N.

Example 9 (c): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (2-hydroxy-ethyl)-amide



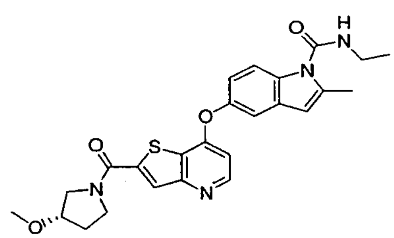
Example 9(c) was prepared in a similar manner as Example 4(g) except that ethanolamine was used instead of methylamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.47 (1H, d, J = 5.4 Hz), 7.91 (1H, d, J = 6.1 Hz), 7.82 (1H, d, J = 8.9 Hz), 7.32 (1H, d, J = 2.2 Hz), 7.03 (1H, dd, J = 2.2, 8.9 Hz), 6.66 (1H, d, J = 5.5 Hz), 6.38 (1H, s), 4.16-3.70 (5H, m), 3.79 (2H, t, J = 5.7 Hz), 3,56 (2H, t, J = 5.7 Hz), 3.38, 3.33 (3H, s), 2.56 (3H, s), 2.30-2.02 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 495, Found 495. Anal. ($C_{25}H_{26}N_4O_5S$•$0.25H_2O$•0.25Hexanes) C, H, N.

Example 9 (d): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid propylamide



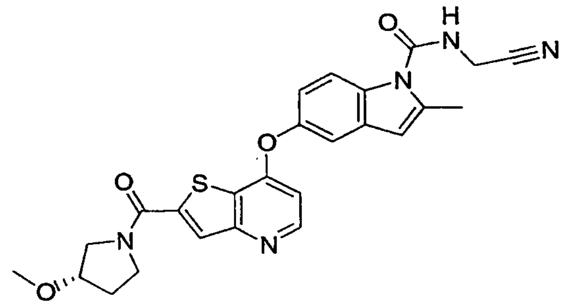
Example 9(d) was prepared in a similar manner as Example 4(g) except that propylamine was used instead of methylamine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (1H, br s), 7.84 (1H, d, J = 9.7 Hz), 7.70 (1H, d, J = 8.9Hz), 7.27 (1H, d, J = 2.3 Hz), 7.00 (1H, dd, J = 2.3, 8.9 Hz), 6.57 (1H, d, J = 4.7 Hz), 6.30 (1H, s), 5.82 (1H, br s), 4.10-3.70 (5H, m), 3.48 (2H, q, J = 6.7 Hz), 3.37, 3.32 (3H, s), 2.58 (3H, s), 2.25-1.90 (2H, m), 1.75 (2H, m), 1.05 (3H, t, J = 7.4 Hz). LCMS (ESI+) [M+H]/z Calc'd 493, Found 493.

Example 9 (e): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid ethylamide



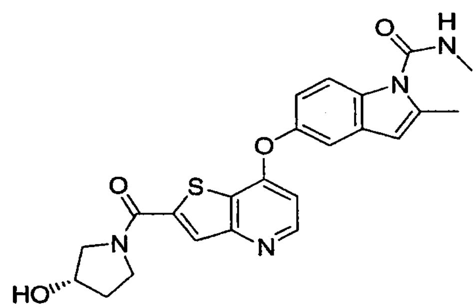
Example 9(e) was prepared in a similar manner as Example 4(g) except that ethylamine was used instead of methylamine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (1H, br s), 7.82 (1H, d, J = 10.6 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.26 (1H, d, J = 2.2 Hz), 6.99 (1H, dd, J = 2.2, 8.8 Hz), 6.56 (1H, d, J = 4.2 Hz), 6.29 (1H, s), 5.89 (1H, br s), 4.15-3.70 (5H, m), 3.55 (2H, m), 3.37, 3.32 (3H, s), 2.58 (3H, s), 2.25-1.90 (2H, m), 1.34 (3H, t, J = 7.2 Hz). LCMS (ESI+) [M+H]/z Calc'd 479, Found 479.

Example 9 (f): 5-[2-(3S-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid cyanomethyl-amide



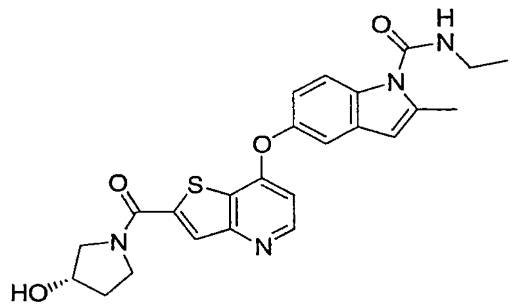
Example 9(f) was prepared in a similar manner as Example 4(g) except that aminoacetonitrile was used instead of methylamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (1H, s), 8.55 (1H, d, J = 3.5 Hz), 8.04 (1H, s), 7.72 (1H, d, J = 8.8 Hz), 7.44 (1H, s), 7.14 (1H, d, J = 8.8 Hz), 6.66 (1H, d, J = 4.2 Hz), 6.47 (1H, s), 4.42 (s, 2H), 4.10-3.70 (5H, m), 3.30 (3H, s), 2.52 (3H, s), 2.01 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 490, Found 490.

Example 9 (g): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid methylamide



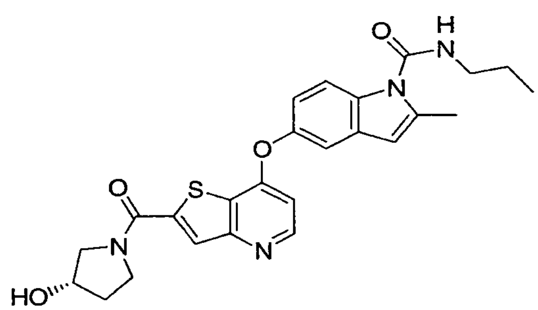
Example 9(g) was prepared in a similar manner as Example 4(n) except that 4(g) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.47 (1H, d, J = 5.7 Hz), 7.91 (1H, d, J = 17.5 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 2.1 Hz), 7.04 (1H, dd, J = 2.1, 8.8Hz), 6.66 (1H, d, J = 5.5 Hz), 6.38 (1H, s), 4.53 (1H, m), 4.10-3.70 (4H, m), 3.01 (3H, s), 2.54 (3H, s), 2.11 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 451, Found 451.

Example 9 (h): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid ethylamide



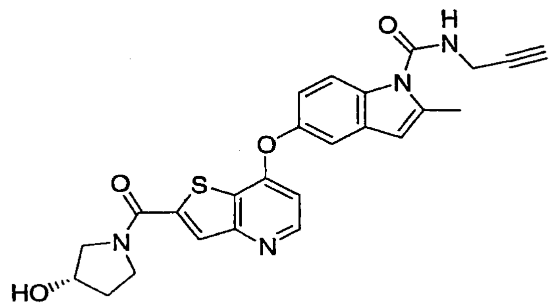
Example 9(h) was prepared in a similar manner as Example 4(n) except that 9(e) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.47 (1H, d, J = 5.5 Hz), 7.91 (1H, d, J = 17.3 Hz), 7.71 (1H, d, J = 8.8 Hz), 7.33 (1H, d, J = 2.1 Hz), 7.04 (1H, dd, J = 2.1, 8.8Hz), 6.66 (1H, d, J = 5.5 Hz), 6.37 (1H, s), 4.50 (1H, m), 4.10-3.68 (4H, m), 3.47 (2H, q, J = 7.2 Hz), 2.54 (3H, s), 2.11 (2H, m), 1.31 (3H, t, J = 7.2 Hz). LCMS (ESI+) [M+H]/z Calc'd 465, Found 465.

Example 9 (i): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid propylamide



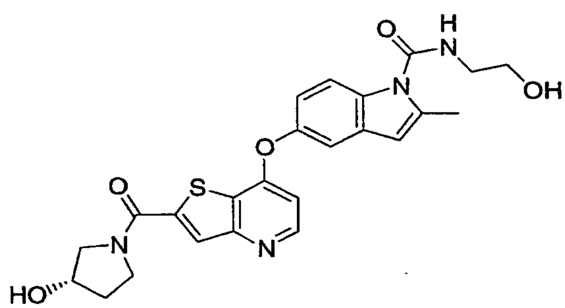
Example 9(i) was prepared in a similar manner as Example 4(n) except that 9(d) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.48 (1H, d, J = 5.5 Hz), 7.92 (1H, d, J = 17.5 Hz), 7.71 (1H, d, J = 8.9 Hz), 7.34 (1H, d, J = 2.3 Hz), 7.05 (1H, dd, J = 2.3, 8.9 Hz), 6.68 (1H, d, J = 5.5 Hz), 6.39 (1H, s), 4.53 (1H, m), 4.10-3.70 (4H, m), 3.40 (2H, t, J = 7.2 Hz), 2.55 (3H, s), 2.11 (2H, m), 1.72 (2H, m), 1.05 (3H, t, J = 7.4 Hz). LCMS (ESI+) [M+H]/z Calc'd 479, Found 479.

Example 9 (j): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid prop-2-ynylamide



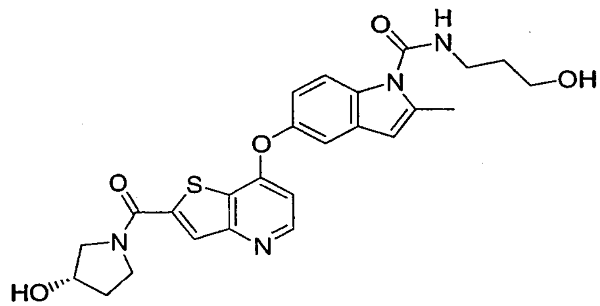
Example 9(j) was prepared in a similar manner as Example 4(n) except that 4(f) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.48 (1H, d, J = 5.5 Hz), 7.92 (1H, d, J = 17.5 Hz), 7.77 (1H, d, J = 8.9 Hz), 7.34 (1H, d, J = 2.3 Hz), 7.06 (1H, dd, J = 2.3, 8.9 Hz), 6.68 (1H, d, J = 5.5 Hz), 6.40 (1H, s), 4.53 (1H, m), 4.22 (2H, d, J = 2.4 Hz), 4.10-3.60 (4H, m), 2.72 (1H, t, J = 2.4 Hz), 2.56 (3H, s), 2.11 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 475, Found 475.

Example 9 (k): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (2-hydroxy-ethyl)-amide



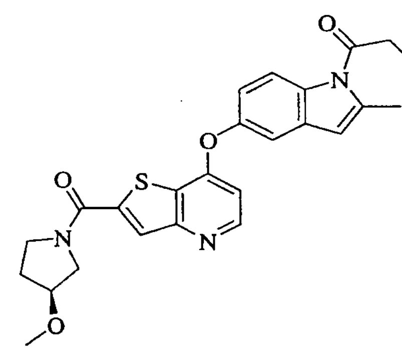
Example 9(k) was prepared in a similar manner as Example 4(n) except that 9(c) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.48 (1H, d, J = 5.7 Hz), 7.92 (1H, d, J = 17.5 Hz), 7.82 (1H, d, J = 8.7 Hz), 7.33 (1H, d, J = 2.1 Hz), 7.04 (1H, dd, J = 2.1, 8.7 Hz), 6.68 (1H, d, J = 5.4 Hz), 6.39 (1H, s), 4.52 (1H, m), 4.02 (2H, m), 3.85-3.60 (4H, m), 3.56 (2H, t, J = 5.6 Hz), 2.57 (3H, s), 2.11 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 481, Found 481.

Example 9 (l): 5-[2-(3S-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-indole-1-carboxylic acid (3-hydroxy-propyl)-amide



Example 9(l) was prepared in a similar manner as Example 4(n) except that 9(b) was used as starting material. ^{1}H NMR (300 MHz, CD_3OD) δ 8.46 (1H, d, J = 5.5 Hz), 7.91 (1H, d, J = 17.3 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.32 (1H, d, J = 2.0 Hz), 7.04 (1H, dd, J = 2.0, 8.8 Hz), 6.66 (1H, d, J = 5.5 Hz), 6.37 (1H, s), 4.53 (1H, m), 4.10-4.00 (2H, m), 3.90-3.65 (4H, m), 3.54 (2H, t, J = 6.8 Hz), 2.55 (3H, s), 2.11 (2H, m), 1.91 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 495, Found 495.

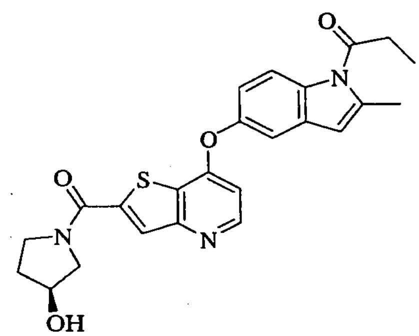
Example 10 (a): 2-{[(3*S*)-3-Methoxypyrrolidin-1-yl]carbonyl}-7-[(2-methyl-1-propionyl-1*H*-indol-5-yl)oxy]thieno[3,2-*b*]pyridine



NaH (0.016 g, 0.4 mmol) was added to a solution of 2-{[(3*S*)-3-methoxypyrrolidin-1-yl]carbonyl}-7-[(2-methyl-1*H*-indol-5-yl)oxy]thieno[3,2-*b*]pyridine (0.108 g, 0.26 mmol) in 2 mL THF. The reaction mixture was stirred at room temperature for 10 min and propanoic anhydride (0.052 mL, 0.4 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and more NaH (0.016 g, 0.4 mmol) and propanoic anhydride (0.052 mL, 0.4 mmol) were added. After 3 h, the reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (2x10 mL). The organic layer was dried and concentrated. The residue was purified by flash column chromatography (0~2 % CH_3OH in CH_2Cl_2) to give a white solid

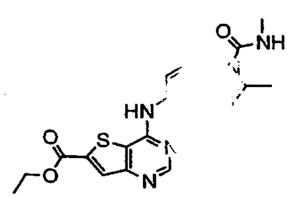
(0.115 g, 95%). ^{1}H NMR (CD_3OD) δ 8.39 (1H, d, *J* = 5.5 Hz), 8.14 (1H, d, *J* = 9.0 Hz), 7.81 (1H, d, *J* = 5.4 Hz), 7.23 (1H, d, *J* = 2.3 Hz), 7.00 (1H, dd, *J* = 2.3, 9.0 Hz), 6.59 (1H, d, *J* = 5.5 Hz), 6.37 (1H, s), 4.04-4.00 (1H, m), 3.95-3.80 (2H, m), 3.73-3.57 (2H, m), 3.27 (1H, d, *J* = 14.3 Hz), 3.00 (2H, q, J = 7.2 Hz), 2.58 (3H, s), 2.20-1.92 (2H, m), 1.21 (3H, t, *J* = 7.2 Hz). Anal. Calc'd for $C_{24}H_{23}N_3O_4S$: C, 64.78; H, 5.44; N, 9.06; Found: C, 64.54; H, 5.67; N, 8.92. ESIMS (MH^+): 464.15.

Example 10 (b): (3*S*)-1-({7-[(2-Methyl-1-propionyl-1*H*-indol-5-yl)oxy]thieno[3,2-*b*]pyridin-2-yl}carbonyl)pyrrolidin-3-ol



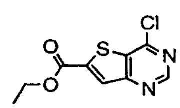
Example 10(b) was prepared in a similar manner as Example 4(n) except that 10(a) was used as starting material. ^{1}H NMR (DMSO-d_6) δ 8.55 (1H, d, *J* = 5.3 Hz), 8.24 (1H, d, *J* = 9.0 Hz), 8.01 (1H, d, *J* = 19.6 Hz), 7.43 (1H, d, *J* = 2.3 Hz), 7.15 (1H, dd, *J* = 2.3, 9.0 Hz), 6.70 (1H, d, *J* = 5.3 Hz), 6.53 (1H, s), 4.36 (1H, d, J = 14.7Hz), 4.01-3.93 (1H, m), 3.67-3.56 (2H, m), 3.35 (2H, m,), 3.10 (2H, q, J = 7.2Hz), 2.65 (3H, s), 2.04-1.80 (2H, m), 1.19 (3H, t, *J* = 7.2 Hz). HRMS Calc'd for $C_{24}H_{23}N_3O_4S$ [MH^+]: 450.1495; Found: 450.1488.

Example 11 (a) S: 4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-*b*]pyrimidine-6-carboxylic acid ethyl ester.



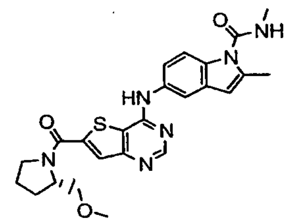
A solution of 4-chloro-thieno[3,2-b]pyrimidine-6-carboxylic acid ethyl ester (0.15g, 0.62 mmol) and 5-amino-2-methyl-indole-1-carboxylic acid methylamide (0.13 g, 065 mmol) in acetonitrile (3 mL) was heated at 100 °C in the microwave for 1h. After cooling to room temperature, the reaction mixture was poured into water 5 (mL). The precipitate that formed was collected by filtration, then triturated from EtOAc (10 mL) and hexane (5 mL) to afford 4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-b]pyrimidine-6-carboxylic acid ethyl ester (0.17 g, 71%) as yellow solid. HPLC: R_t 3.59 min. (96% area). ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.33 (1H, s), 8.72 (1H, s), 8.27 (1H, q, J = 3.5 Hz), 8.67 (1H, q, J = 8.6 Hz), 7.42 (1H, d, J = 8.0 Hz), 6.46 (1H, s), 4.42 (2H, q, J = 8.0), 3.63 (3H, s), 2.94 (3H, d, J = 4.3 Hz), 1.38 (3H, t, J = 5.0 Hz). LCMS (ACPI) (M + H^+) *m/z*: 410.0. Anal. ($C_{20}H_{19}N_5O_3S$•0.35 CH_2Cl_2): Calc'd: C, 55.65; H, 4.52; N, 15.95. Found: C, 55.64; H, 4.59; N, 116.07.

Step (i): 4-Chloro-thieno[3,2-d]pyrimidine-6-carboxylic acid ethyl ester.



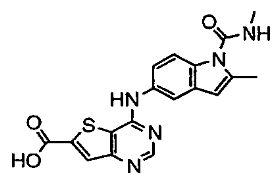
To a solution of 4-chloro-thieno[3,2-b]pyrimidine (1.0g, 5.86 mmol) in THF (20 mL) was added LDA (6.74 mL, 1.0 M) at –78 °C. After stirring for 0.5 h, a solution of ethyl chloroformate (1.7 mL 17.6 mmol) in of THF (10 mL) was added to the reaction mixture. After stirring for an additional 0.5h, the reaction was quenched with 1 mL of CH_3COOH/MeOH (1:1), then diluted with EtOAc (50 mL). The organic layer was washed with 50/50 $NaHCO_3$, dried over $NaHSO_3$ and concentrated. Purification was with silica (50 mL) eluting with Hex/EtOAc, combining purified fraction to afford 4-Chloro-thieno[3,2-b]pyrimidine-6-carboxylic acid ethyl ester (0.64g, 45%) as white solid. HPLC: R_t 4.19 min. (100% area). ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.06 (1H, s), 8.21 (1H, s), 4.49 (2H, q, J = 7.0 Hz), 1.46 (3H, t, J = 7.3 Hz). LCMS (ACPI) (M + H^+) *m/z*: 243.0.

Example 11 (b): 5-[6-(2-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyrimidin-4-ylamino]-2-methyl-indole-1-carboxylic acid methylamide.



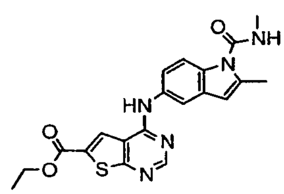
A solution of 4-(2-methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-b]pyrimidine-6-carboxylic acid (0.093g, 0.24 mmol), DIEA (0.10 mL, 0.57 mmol) and HATU (0.12g, 0.31 mmol) in DMF (2 mL) was stirred for 3h. The reaction mixture was partitioned between saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL). The layers were separated and the organic phase was washed with saturated $NaHCO_3$ (50 mL), dried over $NaSO_4$ and concentrated, *in vacuo*. The residue obtained was purified by silica gel chromatography (50 mL), eluting with EtOAc/Hex. (2:1), combining purified fractions which were concentrated, then triturated with MTBE (2 X 2 mL) to afford 5-[6-(2-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyrimidin-4-ylamino]-2-methyl-indole-1-carboxylic acid methylamide (0.074g, 63%). HPLC: R_t 3.50 min. (100% area). ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.77 (1H, s), 8.55 (1H, s), 8.20 (1H, d, J = 4.3 Hz), 7.80 (2H, s), 7.59 (1H, d, 8.6 Hz), 7.34 (1H, 8.8 Hz), 6.38 (1H, s), 4.28 (1H, bs), 3.82-3.75 (2H, m), 3.70-3.60 (2H, m), 3.38 (1H, bs), 3.27 (3H, s), 2.87 (3H, d, J = 4.3 Hz), 2.48 (3H, s), 2.01-1.80 (4H, m). HRMS (ESI) $C_{24}H_{27}N_6O_3S$ $(M + H^+)$ *m/z*: Calc. 479.1865, Found: 479.1881. Anal. ($C_{24}H_{26}N_6O_3S$•0.4 H_2O): Calc'd: C, 59.34; H, 5.56; N, 17.30. Found: C, 59.24; H, 5.46; N, 17.04.

Step (i): 4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-*b*]pyrimidine-6-carboxylic acid:



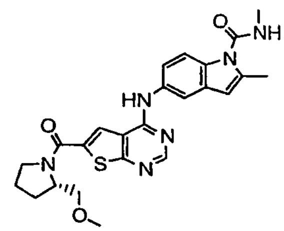
4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-b]pyrimidine-6-carboxylic acid ethyl ester (0.10g, 0.24 mmol) was added to a solution of LiOH (0.011g, 0.28 mmol) in 7 mL of THF/ MeOH /H_2O (0.7:0.0.2:0.1), then stirred for 2h. The mixture was then neutralized by addition of 1N HCl. The precipitate that formed was collected by filtration, then rinsed with H_2O (10 mL) and Et_2O (10 mL) and dried under vacuum to afford 4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-b]pyrimidine-6-carboxylic acid (0.086g, 92%) as yellow solid. HPLC: R_t 3.02 min. (100% area). ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.0 (1H, s), 8.70 (1H, s), 8.34 (1H, d, J = 4.0 Hz), 8.03 (1H, s), 7.93 (1H, s), 7.74 (1H, d, J = 9.1 Hz), 7.49 (1H, s), 6.53 (1H, s), 3.02 (3H, d, J = 5.1 Hz), 2.62 (3H, s). LCMS (ACPI) (M + H^+) *m/z*: 382.0.

Example 12 (a): 4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[2,3-*b*]pyrimidine-6-carboxylic acid ethyl ester.



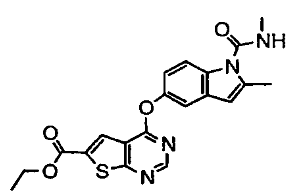
Example 12 (a) was made in similar manner to 11 (a) except that 4-chloro-thieno[2,3-b]pyrimidine-6-carboxylic acid ethyl ester was used instead of 4-chloro-thieno[3,2-b]pyrimidine-6-carboxylic acid ethyl ester. HPLC: R_t 4.08 min. (97% area). ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.11 (1H, s), 8.83 (1H, s), 8.64 (1H, s), 8.27 (1H, d, J = 4.5 Hz), 8.10 (1H,s), 7.71 (1H, d, J = 8.1 Hz), 7.56 (1H, d, J = 7.3 Hz), 6.50 (1H, s), 4.49 (2H, q, J = 7.1 Hz), 3.41 (3H, s), 2.98 (3H, d, J = 4.3 Hz), 1.46 (3H, t, J = 7.1 Hz). HRMS (ESI) $C_{20}H_{20}N_5O_4S$ (M + H^+) *m/z*: Calc. 410.1287, Found: 410.1308. Anal. ($C_{20}H_{19}N_5O_4S$•0.5 H_2O): Calc'd: C, 57.40; H, 4.82; N, 16.74. Found: C, 57.60; H, 4.74; N, 16.50.

Example 12 (b): 5-[6-(2-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[2,3-*b*]pyrimidin-4-ylamino]-2-methyl-indole-1-carboxylic acid methylamide.



Example 12 (b) was made in similar manner to 11 (b) except that 4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[2,3-b]pyrimidine-6-carboxylic acid was used instead of 4-(2-methyl-1-methylcarbamoyl-1H-indol-5-ylamino)-thieno[3,2-b]pyrimidine-6-carboxylic acid. HPLC: R_t 4.08 min. (97% area). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.71 (1H, s), 8.34 (1H, d, J = 4.3 Hz), 8.07 (1H, s), 7.71 (1H, d, J = 8.3 Hz), 7.47 (1H, s), 7.15 (1H, dd, J = 9.1, 2.5 Hz), 6.46 (1H, s), 4.39 (1H, bs), 3.98-3.80 (1H, m), 3.72-3.59 (1H, s), 3.45-3.30 (2H, m), 3.37 (3H, s), 2.96 (1H, d, J = 4.6 Hz), 2.60 (3H, s), 2.05-1.94 (4H, m). HRMS (ESI) $C_{24}H_{26}N_5O_4S$ (M + H^+) *m/z*: Calc. 480.1706, Found: 480.1696. Anal. ($C_{24}H_{25}N_5O_4S$•0.1 EtOAc): Calc'd: C, 60.01; H, 5.33; N, 14.34. Found: C, 60.15; H, 5.43; N, 14.06.

Example 12 (c): 4-(2-Methyl-1-methylcarbamoyl-1H-indol-5-yloxy)-thieno[2,3-*b*]pyrimidine-6-carboxylic acid ethyl ester.



Example 12 (c) was made in similar manner to Example 12 (a) except that 5-hydroxyindole-1-carboxylic acid methylamide and DBU (1 equivalent) was used instead of 5-aminoindole-1-carboxylic acid methylamide. HPLC: R_t 4.59 min. (100% area). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.77 (1H, s), 8.34 (2H, s), 7.72 (1H, d, J = 8.8 Hz), 7.48 (1H, d, J = 2.3 Hz), 7.16 (1H, d, J = 6.6 Hz), 6.47 (1H, s), 4.47 (2H, q, J = 7.1), 3.38 (3H, s), 2.96 (3H, d, J = 5.6 Hz), 1.43 (3H, t, J = 7.1 Hz). HRMS (ESI) $C_{20}H_{19}N_4O_4S$ (M + H^+) *m/z*: Calc. 411.1127, Found:

411.1118. Anal. ($C_{20}H_{18}N_4O_4S{\bullet}0.6\ CH_2Cl_2$): Calc'd: C, 53.62; H, 4.19; N, 12.14. Found: C, 53.35; H, 4.04; N, 12.14.

The exemplary compounds described above may be tested for their activity using the tests described below.

BIOLOGICAL TESTING; ENZYME ASSAYS

The stimulation of cell proliferation by growth factors such as VEFG, FGF, and others is dependent upon their induction of autophosphorylation of each of their respective receptor's tyrosine kinases. Therefore, the ability of a protein kinase inhibitor to block cellular proliferation induced by these growth factors is directly correlated with its ability to block receptor autophosphorylation. To measure the protein kinase inhibition activity of the compounds, the following constructs were devised.

VEGF-R2 Construct for Assay:

This construct determines the ability of a test compound to inhibit tyrosine kinase activity. A construct (VEGF-R2Δ50) of the cytosolic domain of human vascular endothelial growth factor receptor 2 (VEGF-R2) lacking the 50 central residues of the 68 residues of the kinase insert domain was expressed in a baculovirus/insect cell system. Of the 1356 residues of full-length VEGF-R2, VEGF-R2Δ50 contains residues 806-939 and 990-1171, and also one point mutation (E990V) within the kinase insert domain relative to wild-type VEGF-R2. Autophosphorylation of the purified construct was performed by incubation of the enzyme at a concentration of 4 μM in the presence of 3 mM ATP and 40 mM $MgCl_2$ in 100 mM HEPES, pH 7.5, containing 5% glycerol and 5 mM DTT, at 4 °C for 2 h. After autophosphorylation, this construct has been shown to possess catalytic activity essentially equivalent to the wild-type autophosphorylated kinase domain construct. See Parast et al., *Biochemistry*, 37, 16788-16801 (1998).

FGF-R1 Construct for Assay:

The intracellular kinase domain of human FGF-R1 was expressed using the baculovirus vector expression system starting from the endogenous methionine residue 456 to glutamate 766, according to the residue numbering system of Mohammadi et al., *Mol. Cell. Biol.*, 16, 977-989 (1996). In addition, the construct also has the following 3 amino acid substitutions: L457V, C488A, and C584S.

VEGF-R2 Assay

Coupled Spectrophotometric (FLVK-P) Assay

The production of ADP from ATP that accompanies phosphoryl transfer was coupled to oxidation of NADH using phosphoenolpyruvate (PEP) and a system having pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH was monitored by following the decrease of absorbance at 340 nm ($e_{340} = 6.22\ cm^{-1}\ mM^{-1}$) using a Beckman DU 650 spectrophotometer. Assay conditions for phosphorylated VEGF-R2Δ50 (indicated as FLVK-P in the tables below) were the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 5.1 mM poly(E_4Y_1); 1 mM ATP; and 25 mM $MgCl_2$ in 200 mM HEPES, pH 7.5. Assay conditions for unphosphorylated VEGF-R2Δ50 (indicated as FLVK in the tables) were the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 20 mM poly(E_4Y_1); 3 mM ATP; and 60 mM $MgCl_2$ and 2 mM $MnCl_2$ in 200 mM HEPES, pH 7.5. Assays were initiated with 5 to 40 nM of enzyme. K_i values were determined by measuring enzyme activity in the presence of varying concentrations of test compounds. The percent inhibition at 50 nm (% inhibition @ 50 nm) was determined by linear least-squares regression analysis of absorpbance as a function of time. The binding inhibitions were fitted to equation as described by Morrison. The data were analyzed using Enzyme Kinetic and Kaleidagraph software.

FGF-R Assay

The spectrophotometric assay was carried out as described above for VEGF-R2, except for the following changes in concentration: FGF-R = 50 nM, ATP = 2 mM, and poly(E4Y1) = 15 mM.

HUVEC + VEGF Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells ("HUVEC"). HUVEC cells (passage 3-4, Clonetics, Corp.) were thawed into EGM2 culture medium (Clonetics Corp) in T75 flasks. Fresh EGM2 medium was added to the flasks 24 hours later. Four or five days later, cells were exposed to another culture medium (F12K medium supplemented with 10% fetal bovine serum (FBS), 60 μg/mL endothelial cell growth supplement (ECGS), and 0.1 mg/mL heparin). Exponentially-growing HUVEC cells were used in experiments thereafter. Ten to twelve thousand HUVEC cells were plated in 96-well dishes in 100 μl of rich, culture medium (described above). The cells were allowed to attach for 24 hours in this medium. The medium was then removed by

aspiration and 105 μl of starvation media (F12K+1% FBS) was added to each well. After 24 hours, 15 μl of test agent dissolved in 1% DMSO in starvation medium or this vehicle alone was added into each treatment well; the final DMSO concentration was 0.1%. One hour later, 30 μl of VEGF (30 ng/mL) in starvation media was added to all wells except those containing untreated controls; the final VEGF concentration was 6 ng/mL. Cellular proliferation was quantified 72 hours later by MTT dye reduction, at which time cells were exposed for 4 hours MTT (Promega Corp.). Dye reduction was stopped by addition of a stop solution (Promega Corp.) and absorbance at 595 nm was determined on a 96-well spectrophotometer plate reader.

Mouse PK Assay

The pharmacokinetics (e.g., absorption and elimination) of drugs in mice were analyzed using the following experiment. Test compounds were formulated as a suspension in a 30:70 (PEG 400: acidified H_20) vehicle. This solution was administered orally (p.o.) and intraperitoneally (i.p.) at 50 mg/kg to two distinct groups (n=4) of B6 female mice. Blood samples were collected via an orbital bleed at time points: 0 hour (pre-dose), 0.5 hr, 1.0 hr, 2.0 hr, and 4.0 hr post dose. Plasma was obtained from each sample by centrifugation at 2500 rpm for 5 min. Test compound was extracted from the plasma by an organic protein precipitation method. For each time bleed, 50 μL of plasma was combined with 1.0 mL of acetonitrile, vortexed for 2 min. and then spun at 4000 rpm for 15 min. to precipitate the protein and extract out the test compound. Next, the acetonitrile supernatant (the extract containing test compound) was poured into new test tubes and evaporated on a hot plate (25°C) under a steam of N_2 gas. To each tube containing the dried test compound extract, 125 μL of mobile phase (60:40, 0.025 M $NH_4H_2PO_4$ + 2.5 mL/L TEA:acetonitrile) was added. The test compound was resuspended in the mobile phase by vortexing and more protein was removed by centrifugation at 4000 rpm for 5 min. Each sample was poured into an HPLC vial for test compound analysis on an Hewlett Packard 1100 series HPLC with UV detection. From each sample, 95 μL was injected onto a Phenomenex-Prodigy reverse phase C-18, 150 x 3.2 mm column and eluted with a 45-50% acetonitrile gradient run over 10 min. Test-compound plasma concentrations (μg/mL) were determined by a comparison to standard curve (peak area vs. conc. μg/mL) using known concentrations of test compound extracted from plasma samples in the manner described above. Along with the standards and unknowns, three groups (n=4) of quality controls (0.25 μg/mL, 1.5 μg/mL, and 7.5 μg/mL) were run to insure the consistency of the analysis. The standard curve had an $R_2 > 0.99$ and

the quality controls were all within 10% of their expected values. The quantitated test samples were plotted for visual display using Kalidagraph software and their pharmacokinetic parameters were determined using WIN NONLIN software.

Human Liver Microsome (HLM) Assay

Compound metabolism in human liver microsomes was measured by LC-MS analytical assay procedures as follows. First, human liver microsomes (HLM) were thawed and diluted to 5 mg/mL with cold 100 mM potassium phosphate (KPO_4) buffer. Appropriate amounts of KPO_4 buffer, NADPH-regenerating solution (containing B-NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase, and $MgCl_2$), and HLM were preincubated in 13 x 100 mm glass tubes at 37°C for 10 min. (3 tubes per test compound--triplicate). Test compound (5 μM final) was added to each tube to initiate reaction and was mixed by gentle vortexing, followed by incubation at 37°C. At t=0, and 2 h, a 250-uL sample was removed from each incubation tube to separate 12 x 75 mm glass tubes containing 1 mL ice-cold acetonitrile with 0.05 μM reserpine. Samples were centrifuged at 4000 rpm for 20 min. to precipitate proteins and salt (Beckman Allegra 6KR, S/N ALK98D06, #634). Supernatant was transferred to new 12 x 75 mm glass tubes and evaporated by Speed-Vac centrifugal vacuum evaporator. Samples were reconstituted in 200 μL 0.1% formic acid/acetonitrile (90/10) and vortexed vigorously to dissolve. The samples were then transferred to separate polypropylene microcentrifuge tubes and centrifuged at 14000 x g for 10 min. (Fisher Micro 14, S/N M0017580). For each replicate (#1-3) at each timepoint (0 and 2 h), an aliquot sample of each test compound was combined into a single HPLC vial insert (6 total samples) for LC-MS analysis, which is described below.

The combined compound samples were injected into the LC-MS system, composed of a Hewlett-Packard HP1100 diode array HPLC and a Micromass Quattro II triple quadruple mass spectrometer operating in positive electrospray SIR mode (programmed to scan specifically for the molecular ion of each test compound). Each test compound peak was integrated at each timepoint. For each compound, peak area at each timepoint (n=3) was averaged, and this mean peak area at 2 h was divided by the average peak area at time 0 hour to obtain the percent test compound remaining at 2 h.

KDR (VEGFR2) phosphorylation in PAE-KDR cells assay

This assay determines the ability of a test compound to inhibit the autophosphorylation of KDR in porcine aorta endothelial (PAE)-KDR cells. PAE cells that overexpress human KDR were used in this assay. The cells were cultured in Ham's F12

media supplemented with 10% fetal bovine serum (FBS) and 400ug/mL G418. Thirty thousands cells were seeded into each well of a 96-well plate in 75 μL of growth media and allowed to attach for 6 hours at 37°C. Cells were then exposed to the starvation media (Ham's F12 media supplemented with 0.1% FBS) for 16 hours. After the starvation period was over, 10 μL of test agent in 5% DMSO in starvation media were added to the test wells and 10 μL of the vehicle (5% DMSO in starvation media) were added into the control wells. The final DMSO concentration in each well was 0.5%. Plates were incubated at 37°C for 1 hour and the cells were then stimulated with 500 ng/ml VEGF (commercially available from R & D System) in the presence of 2mM Na_3VO_4 for 8 minutes. The cells were washed once with 1 mm Na_3VO_4 in HBSS and lysed by adding 50 μL per well of lysis buffer. One hundred μL of dilution buffer were then added to each well and the diluted cell lysate was transferred to a 96-well goat ant-rabbit coated plate (commercially available from Pierce) which was pre-coated with Rabbit anti Human Anti-flk-1 C-20 antibody (commercially available from Santa Cruz). The plates were incubated at room temperature for 2 hours and washed seven times with 1% Tween 20 in PBS. HRP-PY20 (commercially available from Santa Cruz) was diluted and added to the plate for a 30-minute incubation. Plates were then washed again and TMB peroxidase substrate (commercially available from Kirkegaard & Perry) was added for a 10-minute incubation. One hundred μL of 0.09 N H_2SO_4 was added to each well of the 96-well plates to stop the reaction. Phosphorylation status was assessed by spectrophotometer reading at 450 nm. IC_{50} values were calculated by curve fitting using a four-parameter analysis.

PAE-PDGFRβ phosphorylation in PAE-PDGFRB cells assay

This assay determines the ability of a test compound to inhibit the autophosphorylation of PDGFRβ in porcine aorta endothelial (PAE)- PDGFRβ cells. PAE cells that overexpress human PDGFRβ were used in this assay. The cells were cultured in Ham's F12 media supplemented with 10% fetal bovine serum (FBS) and 400ug/ml G418. Twenty thousands cells were seeded in each well of a 96-well plate in 50 μL of growth media and allowed to attach for 6 hours at 37°C. Cells were then exposed to the starvation media (Ham's F12 media supplemented with 0.1% FBS) for 16 hours. After the starvation period was over, 10 μL of test agent in 5% DMSO in starvation media were added to the test wells and 10 μL of the vehicle (5% DMSO in starvation media) were added into the control wells. The final DMSO concentration in each well was 0.5%. Plates were incubated at 37°C for 1 hour and the cells were then stimulated with 1μg/mL PDGF-BB (R & D System) in the

presence of 2mM Na_3VO_4 for 8 minutes. The cells were washed once with 1 mm Na_3VO_4 in HBSS and lysed by adding 50 μL per well of lysis buffer. One hundred μL of dilution buffer were then added to each well and the diluted cell lysate was transferred to a 96-well goat ant-rabbit coated plate (Pierce), which was pre-coated with Rabbit anti Human PDGFRβ antibody (Santa Cruz). The plates were incubated at room temperature for 2 hours and washed seven times with 1% Tween 20 in PBS. HRP-PY20 (Santa Cruz) was diluted and added to the plate for a 30-minute incubation. Plates were then washed again and TMB peroxidase substrate (Kirkegaard & Perry) was added for a 10-minute incubation. One hundred μL of 0.09 N H_2SO_4 was added into each well of the 96-well plate to stop the reaction. Phosphorylation status was assessed by spectrophotometer reading at 450 nm. IC_{50} values were calculated by curve fitting using a four-parameter analysis.

The results of the testing of the compounds using various assays are summarized in Tables 1 and 2 below, where a notation of "% @" indicates the percent inhibition at the stated concentration.

TABLE 1

Example Number	FLVK (% @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM)	PAE KDR autophos IC50 (nM)	PAE PDGFR autophos IC50 (nM)	bFGF HUVEC IC50 (nM)	Mouse PK AUC, po ng-h/mL	Mouse Cmax, po ng-h/mL
5m	98	0.586	NT	NT	NT	NT	NT	NT
4w	99	0.172	NT	NT	NT	NT	NT	NT
4v	99	0.416	NT	NT	NT	NT	NT	NT
4u	98	0.2	NT	NT	NT	NT	NT	NT
4t	98	0.594	NT	NT	NT	NT	NT	NT
4s	98	0.085	NT	NT	NT	NT	NT	NT
6g	97	1.23	NT	NT	NT	NT	NT	NT
5l	99	0.189	NT	NT	NT	NT	NT	NT
4r	96	0.701	NT	NT	NT	NT	NT	NT
5k	99	0.148	NT	NT	NT	NT	NT	NT
6f	98	0.154	NT	NT	NT	NT	NT	NT
6e	99	0.279	NT	NT	NT	NT	NT	NT
5j	100	0.388	NT	NT	NT	NT	NT	NT
5i	97	0.525	0.11	NT	NT	NT	NT	NT
3h	95	1.194	1.94	NT	NT	225	NT	NT
4q	98	0.475	0.27	0.26	NT	NT	NT	NT
5h	98	0.52	0.28	0.29	9.9	NT	NT	NT
6c	97	0.688	0.99	1.27	32	NT	NT	NT
3g	95	1.117	0.44	2.6	>1000	656	46	19
3f	57	10.52	3.99	1.85	>1000	2053	44	24
6b	99	0.647	1.46	0.952	21.2	NT	NT	NT
6d	99	0.32	0.068; 0.22	0.123, 0.31	29.1	NT	1628	302
5g	99	0.45	0.15; 0.12	NT	11.2	NT	1170	321
5f	100	0.095	0.116; 0.10	0.178	9.9	NT	NT	NT
5e	100	0.431	0.042; 0.56	0.256; 0.52; 0.237	14.1	NT	1961	1101

TABLE 1 (continued)

Example Number	FLVK (% @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM)	PAE KDR autophos IC50 (nM)	PAE PDGFR autophos IC50 (nM)	bFGF HUVEC IC50 (nM)	Mouse PK AUC, po ng-h/mL	Mouse Cmax, po ng-h/mL
5d	96	0.324	0.35	0.53; 0.44; 0.275	21.5	NT	NT	NT
6a	98	0.428	0.427	NT	28.6	NT	NT	NT
5c	99	0.605	0.115	NT	7.7	NT	36246	19734
5b	98	0.504	0.054; 0.42	0.5	13.1	13.6	NT	NT
3i	74	4.17	5.5	NT	NT	NT	NT	NT
5a	99	0.16	0.14	NT	3.8	NT	NT	NT
3e	87	2.1	4.9	NT	NT	NT	NT	NT
4p	98	0.25	0.128	0.22	4.0	NT	4628	2711
1k	97	0.63	0.24; 0.08	2.1; 5.4; 4.74	>1000	26.6	18	8
1j	96	0.72	0.149	NT	NT	NT	NT	NT
1i	93	0.69	1.03	NT	~1000	44.2	NT	NT
4m	99	0.271	0.37	NT	3.8	NT	NT	NT
1e	97	0.51	0.18	0.73; 0.41	11.3	NT	NT	NT
1h	94	1.23	0.114; 0.42	NT	57.7	NT	NT	NT
3d	60	1.11	61.6	2.7; 6.9	>1000	NT	NT	NT
1q	99	0.17	0.481	NT	>1000	NT	6	5
4i	97	1.56	0.569	NT	5.5	NT	NT	NT
4h	91	1.6	0.65	0.116; 0.34; 0.21	19	NT	2604	657
4g	97	0.23	0.139	0.58; 0.98	10.5	NT	3625	2277
1s	98	1.1	0.308	0.42; 0.7	165; 98	NT	NT	NT
1r	93	0.64	0.301	NT	155; 120	NT	NT	NT
4n	99	0.62	0.042	0.35; 0.16; 0.167	5.8	NT	1850	1107
4o	97	0.63	0.071; 0.09	0.012; 0.009	9	7.9	28509	5074
4f	95	0.85	0.057; 0.03	0.149	14; 14	9.1; 43	15629	8840
4l	96	0.19	0.176	0.09	15	NT	321227	11304
4k	96	0.1	NT	0.569	10	5.8	NT	NT

TABLE 1 (continued)

Example Number	FLVK (% @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM)	PAE KDR autophos IC50 (nM)	PAE PDGFR autophos IC50 (nM)	bFGF HUVEC IC50 (nM)	Mouse PK AUC, po ng-h/mL	Mouse Cmax, po ng-h/mL
4j	96	0.121	0.088	0.86; 0.35; 0.34	10; 13	2.5; 4.7	5075	3434
3b	95	0.21	0.181; 0.04	0.32; 0.444	142; 125	7; 27.8	18776	11092
3c	81	0.79	2.33	0.1; 0.041	631	184; 262	0	0
3a	91	0.45	0.245; 0.41	0.72; 0.33; 0.35	84; 99	24.9; 52	10268	3954
1p	93	0.2	0.303; 0.145	NT	56	119	2531	1228
1o	96	0.37	0.34	1.6	533	49.6; 52	219	100
2e	95	0.16	0.5; 0.403	1.32; 1.38	>1000	27.8; 31.6	43	28
1u	NT	NT	>10	NT	>100	4844	NT	NT
1g	NT	NT	1; 0.56; 0.56	NT	95; 152	58.9; 21; 22	NT	NT
1v	10	NT	>10	NT	NT	>1000	1084	725
1n	94	NT	0.64; 0.46	4.01; 2.77	>1000; 2596	30.2; 19.4	12	8
1m	98	NT	0.37	NT	57	5.4	1725	902
1l	94	NT	0.3	NT	49; 45; 95	6.1; 6.1	719	504
1f	97	0.21	0.68	NT	175	NT	1837	1205
4y	10	24	NT	NT	NT	NT	383	265
4x	1	100	NT	NT	NT	NT	NT	NT
4e	96	0.14	0.6	NT	16.7	14	5541	3786
4d	91	0.41	0.8; 4.4; 4.3; 2.86	0.55; 0.37; 0.26	71; 64; 76	246; 121; 267	4064	1963
4c	96	0.1	0.6; 0.05; 0.34; 0.32	0.28; 0.24; 0.36	16; 18; 15	492; 211; 269	8313	2763
4b	97	0.13	0.4; 0.9; 1.0;0.48	0.21; 0.21; 0.25	22; 24; 23	11.7	3638	2112
2d	98	0.32	0.15	NT	11; 25	34	457	411

TABLE 1 (continued)

Example Number	FLVK (% @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM)	PAE KDR autophos IC50 (nM)	PAE PDGFR autophos IC50 (nM)	bFGF HUVEC IC50 (nM)	Mouse PK AUC, po ng-h/mL	Mouse Cmax, po ng-h/mL
2c	97	0.56	0.44; 0.47	0.67; 0.42; 0.42	84; 105; 87	41; 27; 33; 24; 40	6703	3705
1d	97	1.1	0.2; 0.54; 0.56; 0.56; 0.63	0.45; 0.51	42; 45; 74	24; 23.4	5072	2824
1c	98	0.67	0.7	NT	>100; 179	158	616	317
4a	96	1.1	0.2	NT	16.5	33; 34	703	575
1b	88	0.96	0.69	0.28; 0.25	73; 86	80	78	24
1a	90	0.69	0.91	1.06	239	59	1016	526
1t	87	1.13	2.2; 0.12; 0.6; 0.88; 0.57	0.67; 0.35; 0.41	116; >100; 97	126; 123; 51	5862	4652
2b	85	1.03	0.68; 0.46; 0.84; <1.4; 0.05; 0.77	1.42; 1.43; 1.27	856; >100; 616; 556; 657; 682	100; 27; 65	2795	1895
2a	84	2.1	0.3; 0.1; 0.1; 0.2; 0.23; 0.29	0.36; 0.28; 0.32	57; 96; 61; 41	331; 24; 368; 26	1168	1011
2g	82	29.6	>33.3	NT	NT	NT	542	252
2f	2		>10; >100	NT	NT	NT	10600	7700

TABLE 1 (continued)

Example Number	FLVK (% @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM)	PAE KDR autophos IC50 (nM)	PAE PDGFR autophos IC50 (nM)	bFGF HUVEC IC50 (nM)	Mouse PK AUC, po ng-h/mL	Mouse Cmax, po ng-h/mL
3j	95	0.326	0.1	0.27	32	NT	NT	NT
3k	100	0.071	0.01; 0.194	0.3	18.4	NT	NT	NT
3l	97	0.462	0.16	NT	8.1; 6.3	101	NT	NT
3m	83	0.2	NT	NT	2.48	NT	NT	NT
3n	88	0.505	0.267	NT	76.3	87	NT	NT
3o	93	1.35	0.24; 0.48	0.43; 0.52	599	246; 126	2881	2821
3p	81	0.98	0.33	NT	212	227	NT	NT
3q	NT	NT	NT	NT	NT	NT	NT	NT
5n	100	0.12	0.076; 0.182	0.28; 0.5; 0.53	18.2	93	2556	1824
5o	99	0.09	NT	NT	3.65	NT	NT	NT
5p	100	0.083	NT	0.35	4.6	NT	NT	NT
6h	98	0.142	NT	NT	NT	NT	NT	NT
7a	93	0.796	NT	NT	NT	NT	NT	NT
7b	95	0.406	NT	NT	>1000	NT	NT	NT
7c	97	1.911	NT	NT	NT	NT	NT	NT
7d	96	0.504	0.074; 0.28	0.26	62	NT	NT	NT
8a	68	4.55	NT	NT	>1000	NT	NT	NT
8b	97	0.202	NT	0.24	NT	NT	NT	NT
8c	98	0.123	NT	NT	NT	NT	NT	NT
8d	99	0.109	NT	NT	NT	NT	NT	NT
8e	98	0.115	NT	NT	NT	NT	NT	NT
8f	99	0.35	NT	NT	NT	NT	NT	NT
8g	99	0.643	0.15	NT	15.4	9	NT	NT
8h	99	0.301	0.16; 0.2	NT	19	15, 33, 67	2393	920
8i	99	0.477	0.17; 0.25	NT	26, 34	73, >100, 166	NT	NT
8j	99	0.142	NT	NT	NT	NT	NT	NT
8k	95	0.868	0.32	NT	NT	18	NT	NT
8l	88	0.88	1.5	NT	18.8	63	NT	NT

TABLE 1 (continued)

Example Number	FLVK (% @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM)	PAE KDR autophos IC50 (nM)	PAE PDGFR autophos IC50 (nM)	bFGF HUVEC IC50 (nM)	Mouse PK AUC, po ng-h/mL	Mouse Cmax, po ng-h/mL
8m	99	0.004	0.084	NT	4.5	NT	NT	NT
8n	97	0.089	0.03; 0.12; 0.195	NT	10.2	58	NT	NT
8o	74	4.471	1.25	NT	NT	61	NT	NT
8p	98	0.143	0.137	NT	13	197	NT	NT
8q	97	0.286	0.19	0.45; 0.19	29, 13	95	31323	10374
9a	89	0.521	NT	NT	NT	NT	NT	NT
9b	97	0.488	0.33	0.67	60	NT	NT	NT
9c	81	3.24	NT	1.44; 1.1	56	NT	NT	NT
9d	99	0.228	NT	1.47	25	143	NT	NT
9e	99	0.105	NT	0.24	26	NT	NT	NT
9f	84	0.667	0.68	NT	13	NT	NT	NT
9g	98	0.243	0.34; 0.48; 0.8	0.29; 0.86; 0.34	27; 33	45, 40	9529	4537
9h	99	0.258	0.9	NT	31	NT	NT	NT
9i	98	0.245	0.37	0.33	36	5	9477	2321
9j	97	0.162	0.29	NT	18, 20	81	NT	NT
9k	90	0.932	0.49	1.0	274	NT	1104	371
9l	97	0.327	0.27	0.76; 0.51	216	37.6	138	56
10a	64	4.696	0.79	1.2	NT	21	NT	NT
10b	90	2.723	NT	NT	NT	NT	NT	NT
11a	20	37.8	NT	NT	NT	NT	NT	NT
11b	18	28.8	NT	NT	NT	NT	NT	NT
12a	0	240	NT	NT	NT	NT	NT	NT
12b	5	141	NT	NT	>1000	NT	NT	NT
12c	14	34.3	NT	NT	NT	NT	NT	NT

TABLE 2

Example Number	Mouse Cmin, po (ng/mL)	% remain (HLM-UDPGA, 0.5h)	% remain (HLM-NADPH, 0.5h)
5m	NT	NT	NT
4w	NT	NT	NT
4v	NT	NT	NT
4u	NT	NT	NT
4t	NT	NT	NT
4s	NT	NT	NT
6g	NT	NT	NT
5l	NT	NT	NT
4r	NT	NT	NT
5k	16470	5209	940
6f	NT	NT	NT
6e	NT	NT	NT
5j	NT	NT	NT
5i	NT	NT	NT
3h	NT	NT	NT
4q	NT	NT	NT
5h	NT	NT	NT
6c	NT	NT	NT
3g	2	NT	NT
3f	2	NT	NT
6b	NT	NT	NT
6d	125	NT	NT
5g	65	NT	NT
5f	NT	NT	NT
5e	19	NT	NT

TABLE 2 (continued)

Example Number	Mouse Cmin, po (ng/mL)	% remain (HLM-UDPGA, 0.5h)	% remain (HLM-NADPH, 0.5h)
5d	NT	NT	NT
6a	NT	NT	NT
5c	474	NT	NT
5b	NT	NT	NT
3i	NT	NT	NT
5a	NT	NT	NT
3e	NT	NT	NT
4p	68	NT	NT
1k	0	NT	NT
1j	NT	NT	NT
1i	NT	NT	NT
4m	NT	NT	NT
1e	NT	NT	NT
1h	NT	NT	NT
3d	NT	NT	NT
1q	0	NT	NT
4i	NT	NT	NT
4h	161	NT	NT
4g	20	NT	NT
1s	NT	NT	NT
1r	NT	NT	NT
4n	45	NT	NT
4o	825	NT	NT
4f	112	NT	NT
4l	9020	NT	NT
4k	NT	NT	NT

TABLE 2 (continued)

Example Number	Mouse Cmin, po (ng/mL)	% remain (HLM-UDPGA, 0.5h)	% remain (HLM-NADPH, 0.5h)
4j	32	NT	NT
3b	252	NT	NT
3c	0	NT	NT
3a	408	NT	NT
1p	34	NT	NT
1o	6	NT	NT
2e	0	NT	NT
1u	NT	NT	NT
1g	NT	NT	NT
1v	7	NT	NT
1n	0	NT	NT
1m	27	NT	NT
1l	5	NT	NT
1f	4	NT	NT
4y	11	NT	NT
4x	NT	NT	NT
4e	23	NT	NT
4d	54	NT	NT
4c	313	NT	76.1
4b	108	NT	70.9
2d	0	NT	NT
2c	35	NT	76.2
1d	32	NT	85
1c	7	NT	NT
4a	3	NT	NT
1b	5	NT	NT
1a	3	NT	NT
1t	4	NT	76.3
2b	10	104.8	92.1
2a	19	101.8	91.1
2g	6	113.4	106
2f	163	119.4	70.9

TABLE 2 (continued)

Example Number	Mouse Cmin, po (ng/mL)	% remain (HLM-UDPGA, 0.5h)	% remain (HLM-NADPH, 0.5h)
3j	NT	NT	NT
3k	NT	NT	NT
3l	NT	NT	NT
3m	NT	NT	NT
3n	NT	NT	NT
3o	20	NT	NT
3p	NT	NT	NT
3q	NT	NT	NT
5n	47	NT	NT
5o	NT	NT	NT
5p	NT	NT	NT
6h	NT	NT	NT
7a	NT	NT	NT
7b	NT	NT	NT
7c	NT	NT	NT
7d	NT	NT	NT
8a	NT	NT	NT
8b	NT	NT	NT
8c	NT	NT	NT
8d	NT	NT	NT
8e	NT	NT	NT
8f	NT	NT	NT
8g	NT	NT	NT
8h	204	NT	NT
8i	NT	NT	NT
8j	NT	NT	NT

TABLE 2 (continued)

Example Number	Mouse Cmin, po (ng/mL)	% remain (HLM-UDPGA, 0.5h)	% remain (HLM-NADPH, 0.5h)
8k	NT	NT	NT
8l	NT	NT	NT
8m	NT	NT	NT
8n	NT	NT	NT
8o	NT	NT	NT
8p	NT	NT	NT
8q	1297	NT	NT
9a	NT	NT	NT
9b	NT	NT	NT
9c	NT	NT	NT
9d	NT	NT	NT
9e	NT	NT	NT
9f	NT	NT	NT
9g	222	NT	NT
9h	NT	NT	NT
9i	461	NT	NT
9j	NT	NT	NT
9k	43	NT	NT
9l	4	NT	NT
10a	NT	NT	NT
10b	NT	NT	NT
11a	NT	NT	NT
11b	NT	NT	NT
12a	NT	NT	NT
12b	NT	NT	NT
12c	NT	NT	NT

The exemplary compounds described above may be formulated into pharmaceutical compositions according to the following general examples.

Example 1: Parenteral Composition

To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula I is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example 2: Oral Composition

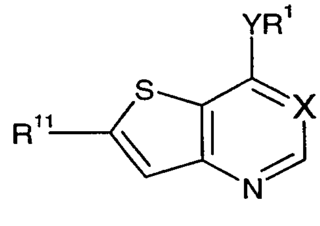
To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula I is mixed with 750 mg of lactose. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

It is to be understood that the foregoing description is exemplary and explanatory in nature, and is intended to illustrate the invention and its preferred embodiments. Through routine experimentation, the artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

CLAIMS

We claim:

1. A compound represented by the formula **I**



I

wherein

X is –CH- or –N-;

Y is –NH-, -O-, -S-, or –CH_2-;

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -C(O)(C_1-C_6 alkyl), C_6-C_{10} aryl or a 5 to 13 membered heterocyclic, wherein said C_6-C_{10} aryl and 5 to 13 membered heterocyclic groups are unsubstituted or substituted with 1 to 5 R^5 substituents;

each R^5 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -NR^6C(O)R^7, -C(O)NR^6R^7, -NR^6R^7, -OR^9, -SO_2NR^6R^7, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_3-C_{10} cycloalkyl, -$(CH_2)_j$O$(CH_2)_q$NR^6R^7, -$(CH_2)_t$O$(CH_2)_q$OR^9, -$(CH_2)_t$OR^9, -S(O)$_j$(C_1-C_6 alkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$O$(CH_2)_j$(C_6-C_{10} aryl), -$(CH_2)_t$O$(CH_2)_q$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_j$N$R^7$$(CH_2)_qNR^6R^7$, -$(CH_2)_jNR^7$$CH_2$C(O)N$R^6R^7$, -$(CH_2)_jNR^7$$(CH_2)_qNR^9$C(O)$R^8$, -$(CH_2)_jNR^7$$(CH_2)_tO(CH_2)_qOR^9$, -$(CH_2)_jNR^7$$(CH_2)_q$S(O)$_j$($C_1$-$C_6$ alkyl),
-$(CH_2)_j$N$R^7$$(CH_2)_t$$R^6$, -$SO_2$$(CH_2)_t$($C_6$-$C_{10}$ aryl), and -$SO_2$$(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the -$(CH_2)_q$- and -$(CH_2)_t$- moieties of the said R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 6, and the alkyl, aryl and heterocyclic moieties of the said R^5 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -NR^6C(O)R^7, -C(O)NR^6R^7, -$(CH_2)_t$NR^6R^7, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic),

$-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

each R^6 and R^7 is independently selected from H, OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tCN(CH_2)_tOR^9$, $-(CH_2)_tCN(CH_2)_tR^9$ and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H, $-OR^6$, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl; and,

R^{11} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)NR^{12}R^{13}$, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tNR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$ and $-CO_2R^{12}$, wherein t is an integer from 0 to 6, wherein said C_1-C_6 alkyl, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic) moieties of the said R^{11} groups are unsubstituted or substituted by one or more R^5 groups;

each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^5, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl

rings are unsubstituted or substituted with one or more R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen;

or prodrugs thereof, or pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

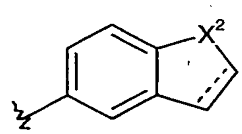
2. A compound of claim 1, wherein R^{11} is $-C(O)NR^{12}R^{13}$, and wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidin-1-yl ring, wherein said pyrrolidin-1-yl ring is unsubstituted or substituted with 1 to 5 R^5 substituents.

3. A compound of claim 2, wherein R^{11} is a $-(CH_2)_t$(5 to 10 membered heterocyclic) group, wherein t is an integer from 0 to 6, said $-(CH_2)_t$(5 to 10 membered heterocyclic) group is unsubstituted or substituted with 1 to 5 R^5 groups.

4. A compound of claim 2, wherein R^{11} is a thiazolyl unsubstituted or substituted by 1 to 5 R^5 groups.

5. A compound of claim 2, wherein R^{11} is an imidazolyl unsubstituted or substituted by 1 to 5 R^5 groups.

6. A compound of claim 1, wherein R^1 is a group represented by the formulas



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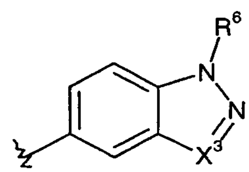

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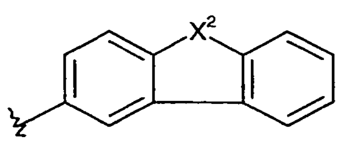

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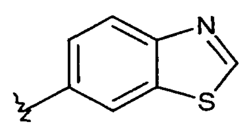
or



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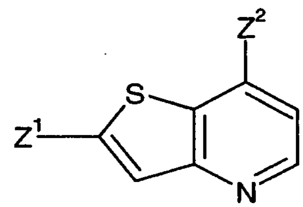
wherein X^2 is -S- or $-N(R^6)-$, X^3 is N or CH, the dashed line in formula **3** represents an optional double bond, and the above R^1 groups of formulas **3** and **5** are unsubstituted or substituted by 1 to 5 R^5 substituents and the R^1 groups of formulas **4** and **6** are unsubstituted or substituted by 1 to 3 R^5 substituents.

7. A compound represented by the formula **II**



II

and to pharmaceutically acceptable salts thereof, wherein:

Z^1 is halo, $-CO_2H$, $-CONH_2$, $CSNH_2$ and Z^2 is $-OR^1$; or

Z^1 is R^{11} and Z^2 is halo; or

Z^1 and Z^2 are each independently halo;

wherein R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)(C_1$-C_6 alkyl), C_6-C_{10} aryl or 5 to 13 membered heterocyclic, wherein said C_6-C_{10} aryl and 5 to 13 membered heterocyclic groups are unsubstituted or substituted by 1 to 5 R^5 substituents;

each R^5 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^9$, $-SO_2NR^6R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_jO(CH_2)_qNR^6R^7$, $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, $-S(O)_j(C_1$-C_6 alkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_tO(CH_2)_j(C_6$-C_{10} aryl), $-(CH_2)_tO(CH_2)_q$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_jNR^7(CH_2)_qNR^9C(O)R^8$, $-(CH_2)_jNR^7(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_jNR^7(CH_2)_qS(O)_j(C_1$-$C_6$ alkyl),

$-(CH_2)_jNR^7(CH_2)_tR^6$, $-SO_2(CH_2)_t(C_6$-C_{10} aryl), and $-SO_2(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the $-(CH_2)_q-$ and $-(CH_2)_t-$ moieties of the said R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 6, and the alkyl, aryl and heterocyclic moieties of the said R^5 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_tNR^6R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

each R^6 and R^7 is independently selected from H, OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, -

$(CH_2)_tCN(CH_2)_tOR^9$, $-(CH_2)_tCN(CH_2)_tR^9$ and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

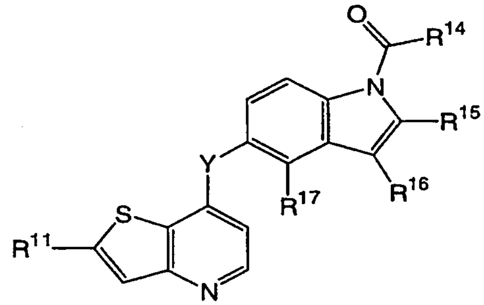
each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H, $-OR^6$, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl; and,

R^{11} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)NR^{12}R^{13}$, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tNR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$ and $-CO_2R^{12}$, wherein t is an integer from 0 to 6, wherein said R^{11} groups C_1-C_6 alkyl, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic) moieties of the said R^{11} groups are unsubstituted or substituted by one or more R^5 groups, and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^5, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl rings are unsubstituted or substituted with one or more R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen;

or prodrugs thereof, or pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

8. A compound represented by the formula **III**



III

wherein:

Y is –NH-, -O-, -S-, -CH_2-;

R^{14} is C_1-C_6 alkyl, C_1-C_6 alkylamino, C_3-C_{10} cycloalkylamino, or methylureido;

R^{15}, R^{16} and R^{17} are independently H, halo, or C_1-C_6 alkyl group; and

R^{11} is a heteroaryl group unsubstituted or substituted by one or more halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -NR^6C(O)R^7, -C(O)NR^6R^7, -NR^6R^7, -OR^9, -SO_2NR^6R^7, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_j$O$(CH_2)_q$NR^6R^7, -$(CH_2)_t$O$(CH_2)_q$OR^9, -$(CH_2)_t$OR^9, -S$(O)_j$(C_1-C_6 alkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$O$(CH_2)_j$(C_6-C_{10} aryl), -$(CH_2)_t$O$(CH_2)_q$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_j$N$R^7$$(CH_2)_qNR^6R^7$, -$(CH_2)_jNR^7$$CH_2$C(O)N$R^6R^7$, -$(CH_2)_jNR^7$$(CH_2)_qNR^9$C(O)$R^8$, -$(CH_2)_jNR^7$$(CH_2)_tO(CH_2)_qOR^9$, -$(CH_2)_jNR^7$$(CH_2)_qS(O)_j$($C_1$-$C_6$ alkyl), -$(CH_2)_j$NR^7 -$(CH_2)_t$$R^6$, -$SO_2$$(CH_2)_t$($C_6$-$C_{10}$ aryl), and -$SO_2$$(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the -$(CH_2)_q$- and -$(CH_2)_t$- moieties of the said R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 6, and the alkyl, aryl and heterocyclic moieties of the said R^5 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -NR^6C(O)R^7, -C(O)NR^6R^7, -$(CH_2)_t$NR^6R^7, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_t$O$(CH_2)_q$OR^9, and -$(CH_2)_t$OR^9, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

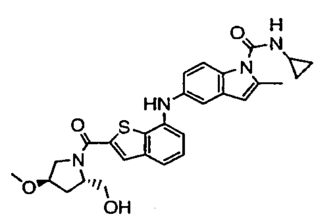
each R^6 and R^7 is independently selected from H, OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_t$O$(CH_2)_q$OR^9, -$(CH_2)_t$CN$(CH_2)_t$OR^9, -$(CH_2)_t$CN$(CH_2)_t$$R^9$ and -$(CH_2)_t$OR^9, wherein t is an integer from 0 to 6

and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl; or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

9. A compound of claim 1 wherein said compound is selected from the group consisting of:



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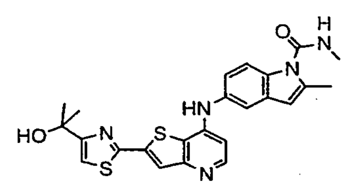

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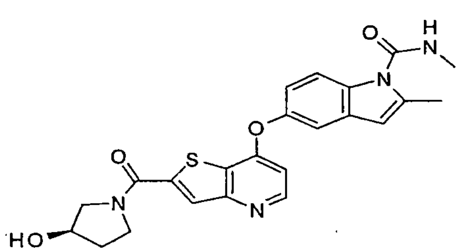

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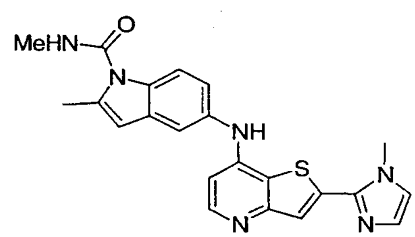

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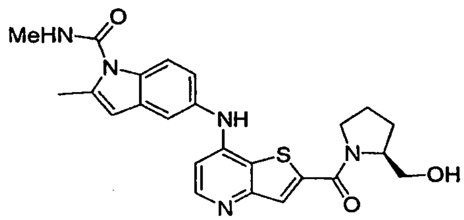

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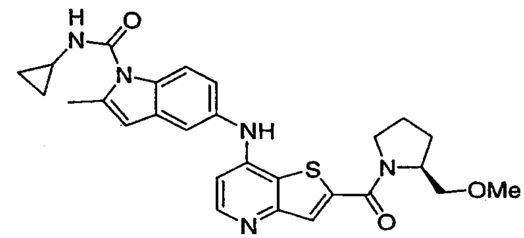

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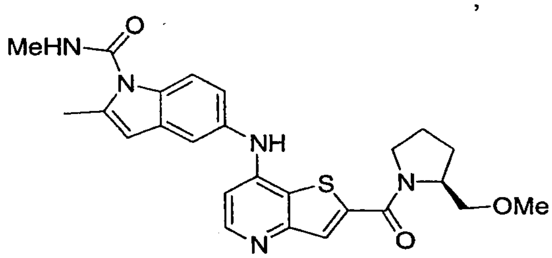

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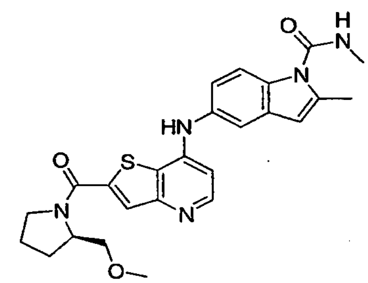

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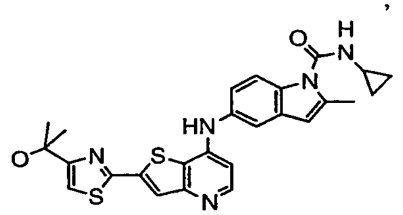

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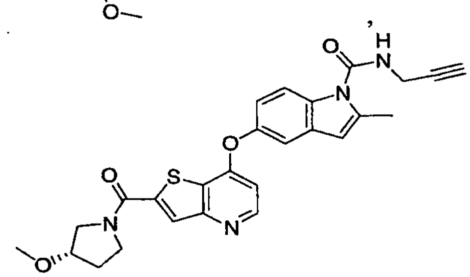

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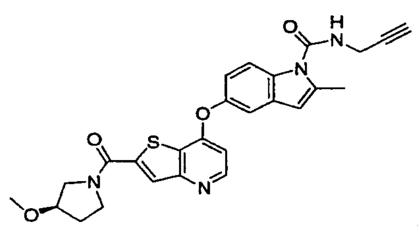

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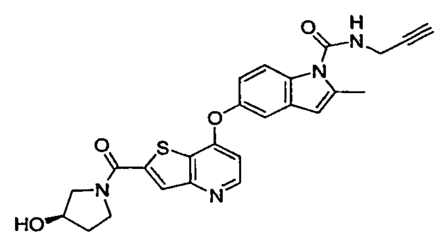

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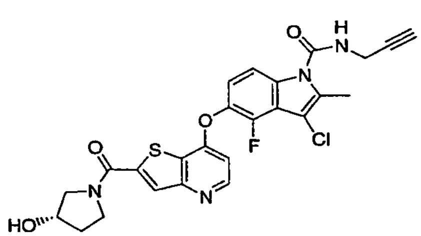


,

or prodrugs thereof, or pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

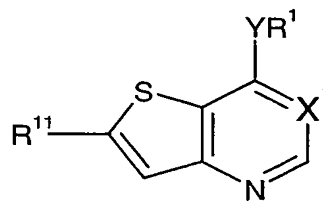
10. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound of claim 1 in combination with an anti-tumor agent.

12. A pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

13. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1.

14. A compound represented by the formula **I**



I

wherein

X is –CH-;

Y is –NH-, or –O-;

R^1 is a 5 to 13 membered heterocyclic substituted with 1 to 5 R^5 substituents;

each R^5 is independently selected from halo, $-C(O)OR^8$, $-C(O)NR^6R^7$, C_1-C_6 alkyl, $-(CH_2)_tOR^9$, and the alkyl moieties of the said R^5 groups are unsubstituted or substituted with $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6;

each R^6 and R^7 is independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_tCN(CH_2)_tOR^9$, and $-(CH_2)_tCN(CH_2)_tR^9$, and the alkyl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with cyano;

each R^8 is a C_1-C_{10} alkyl;

each R^9 and R^{10} is independently selected from H, $-OR^6$, C_1-C_6 alkyl; and,

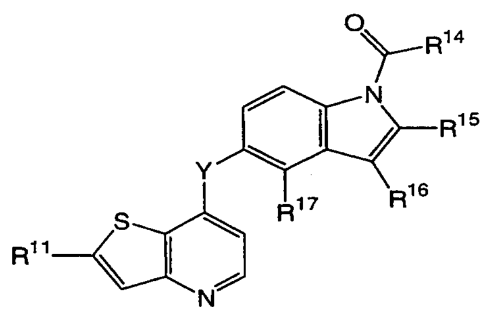
R^{11} is $-C(O)NR^{12}R^{13}$, $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein C_1-C_6 alkyl, -$C(O)(C_6$-C_{10} aryl), $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic) moieties of the said R^{11} groups are unsubstituted or substituted by one or more R^5 groups;

each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^5;

or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 pyrrolidinyl ring substituted with one or more R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen;

or prodrugs thereof, or pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

15. A compound represented by the formula **III**



III

wherein:

Y is –NH-, -O-;

R^{14} is C_1-C_6 alkylamino, C_3-C_{10} cycloalkylamino, or methylureido;

R^{15}, R^{16} and R^{17} are independently H or C_1-C_6 alkyl group; and

R^{11} is a heterocyclic or a heteroaryl group unsubstituted or substituted by one or more groups selected from $-C(O)OR^8$, C_1-C_6 alkyl, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 is independently selected from H, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl;

or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant (*for all designated States except US*): **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **KANIA, Robert, Steven** [US/US]; Agouron Pharmaceuticals Inc.,, A Pfizer Company,, 10777 Science Center Drive, San Diego, CA 92121 (US). **ROMINES, William, Henry III** [US/US]; Agouron Pharmaceuticals Inc.,, A Pfizer Company,, 10777 Science Center Drive, San Diego, CA 92121 (US). **CRIPPS, Stephan, James** [US/US]; Agouron Pharmaceticals Inc.,, A Pfizer Company,, 10777 Science Center Drive, San Diego, CA 92121 (US). **HE, Mingying** [CN/US]; Agouron Pharmaceuticals Inc.,, A Pfizer Company,, 10777 Science Center Drive,, San Diego, CA 92121 (US). **LOU, Jihong** [CN/US]; Agouron Pharmaceuticals Inc.,, A Pfizer Company,, 10777 Science Center Drive, San Diego, CA 92121 (US). **ZHOU, Ru** [CN/US]; Agouron Pharmaceuticals Inc.,, A Pfizer Company, 10777 Science Center Drive, San Diego, CA 92121 (US).

(74) Agent: **LUMB, J., Trevor**; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

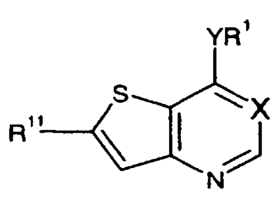
Published:
— *with international search report*

(88) Date of publication of the international search report: 24 December 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/074529 A3

(54) Title: INDOLYL-UREA DERIVATIVES OF THIENOPYRIDINES USEFUL AS ANTI-ANGIOGENIC AGENTS



(I)

(57) Abstract: The invention relates to compounds represented by the formula FI and to prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds or said prodrugs, wherein X, R^1 and R^{11} are as defined herein. The invention also relates to pharmaceutical compositions containing the compounds of formula I and to methods of treating hyperproliferative disorders in a mammal by administering the compounds of formula I.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/00740

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/4365 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 94353 A (LUZZIO MICHAEL JOSEPH ;MARX MATTHEW ARNOLD (US); YANG BINGWEI VERA) 13 December 2001 (2001-12-13) examples 1,21B,33,34,42,43,47,48,51-57,60,67C,68,69,70C,77B examples 78B,79B,80B,81B,82B,ETC -----	1,2,6, 10-13
P,X	WO 03 000194 A (AUTRY CHRISTOPHER L ;MARX MATTHEW A (US); PFIZER (US); LUZZIO MICH) 3 January 2003 (2003-01-03) example 1 -----	1,2,6, 10-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2003	15. 09. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/00740

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-2 (in part), 6-15 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The scope of claims 1,2,6-15 in as far as the expression "prodrug" is concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to this expression.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 (in part), 2, 6, 7 (in part), 9-14 (in part)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1 (in part), 2, 6,7 (in part), 9-14 (in part)

   Compounds of formula I and II in which R11 is C(O)NR12R13 as defined in claim 2 of the present application and pharmaceutical compositions and respective uses of compounds of Formula I

   ---

2. claims: 1 (in part), 4, 6-8 (in part), 9-15 (in part)

   Compounds of formula I, II and III in which R11 is thiazolyl (substituted or unsubstituted) as defined in claim 4 of the present application and pharmaceutical compositions and respective uses of compounds of Formula I and compounds of Formula II in which Z1 and Z2 are each independently halo

   ---

3. claims: 1 (in part), 5, 6-8 (in part), 9-15 (in part)

   Compounds of formula I, II and III in which R11 is unsubstituted or substituted imidazolyl as defined in claim 5 of the present application and pharmaceutical compositions and respective uses of compounds of Formula I

   ---

4. claims: 1 (in part), 3, 6-8 (in part), 10-15 (in part)

   Compounds of formula I, II and III in which R11 is a(n) (un)substituted (CH2)t(5-10 membered heterocyclic group), wherein t is an integer from 0 to 6 as defined in claim 3 and pharmaceutical compositions and respective uses of compounds of Formula I as long as they do not belong to subject 2 or 3

   ---

5. claims: 1 (in part), 7 (in part), 10-15 (in part)

   Compounds of formula I and II and their pharmaceutical compositions and respective uses of compounds of Formula I as long as they are not part of subjects 1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 03/00740

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0194353	A	13-12-2001	AU	5246301 A	17-12-2001
			BR	0111377 A	03-06-2003
			CA	2411084 A1	13-12-2001
			EP	1287001 A1	05-03-2003
			WO	0194353 A1	13-12-2001
			US	2002042409 A1	11-04-2002
WO 03000194	A	03-01-2003	WO	03000194 A2	03-01-2003